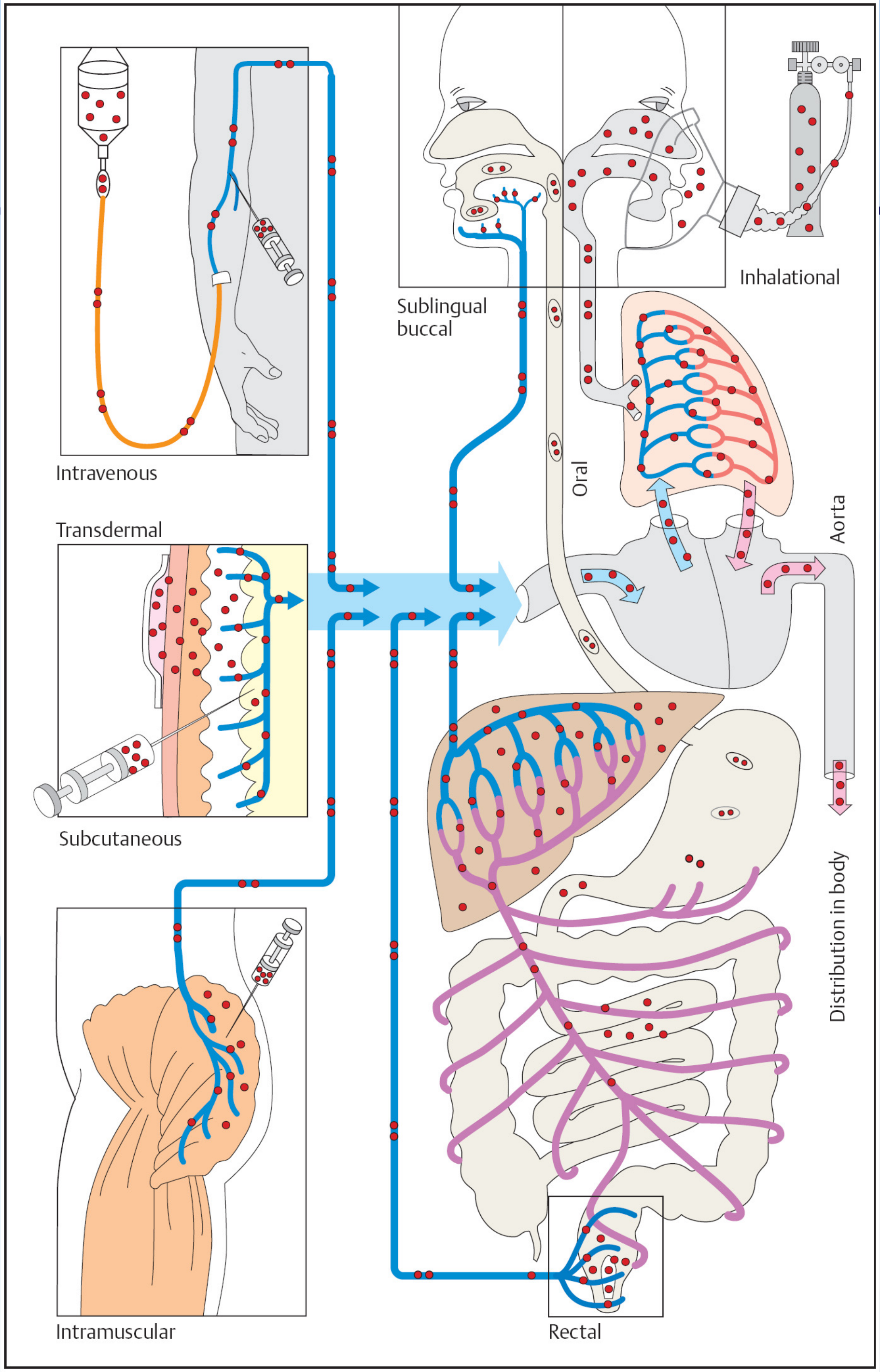
Section II
Autonomic Drugs

References
Basic & Clinical Pharmacology - 11th Ed
Katzung & Trevor's Pharmacology Examination and Board Review, Ninth Edition
Lippincott's Illustrated Reviews Pharmacology, 4th Edition
Color Atlas of Pharmacology 3rd Ed


Intravenous
Transdermal
Subcutaneous
Intramuscular
Sublingual
buccal
Inhalational
Oral
Aorta
Distribution in body
Rectal

Contents

Autonomic drugs

Chapter 6. Introduction to Autonomic Pharmacology

Chapter 7. Cholinoceptor-Activating & Cholinesterase-Inhibiting Drugs

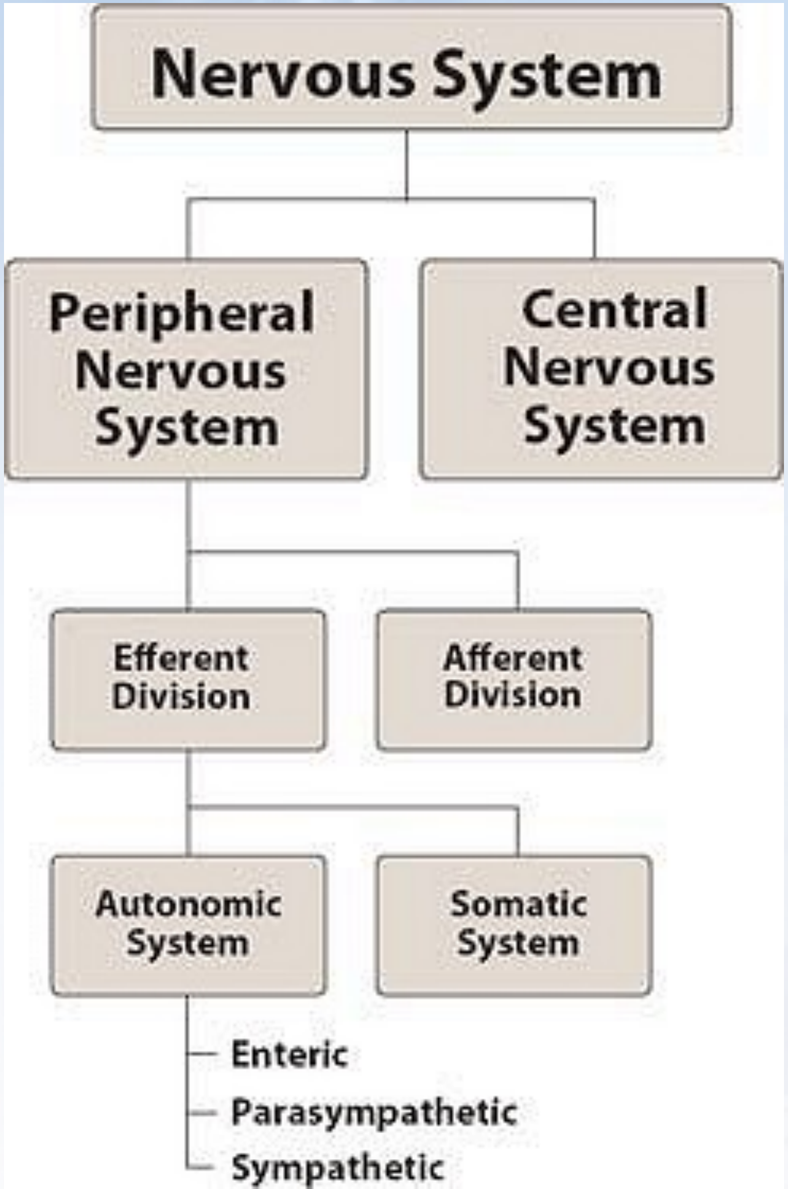
Chapter 8. Cholinoceptor-Blocking Drugs

Chapter 9. Adrenoceptor Agonists & Sympathomimetic Drugs

Chapter 10. Adrenoceptor Antagonist Drugs

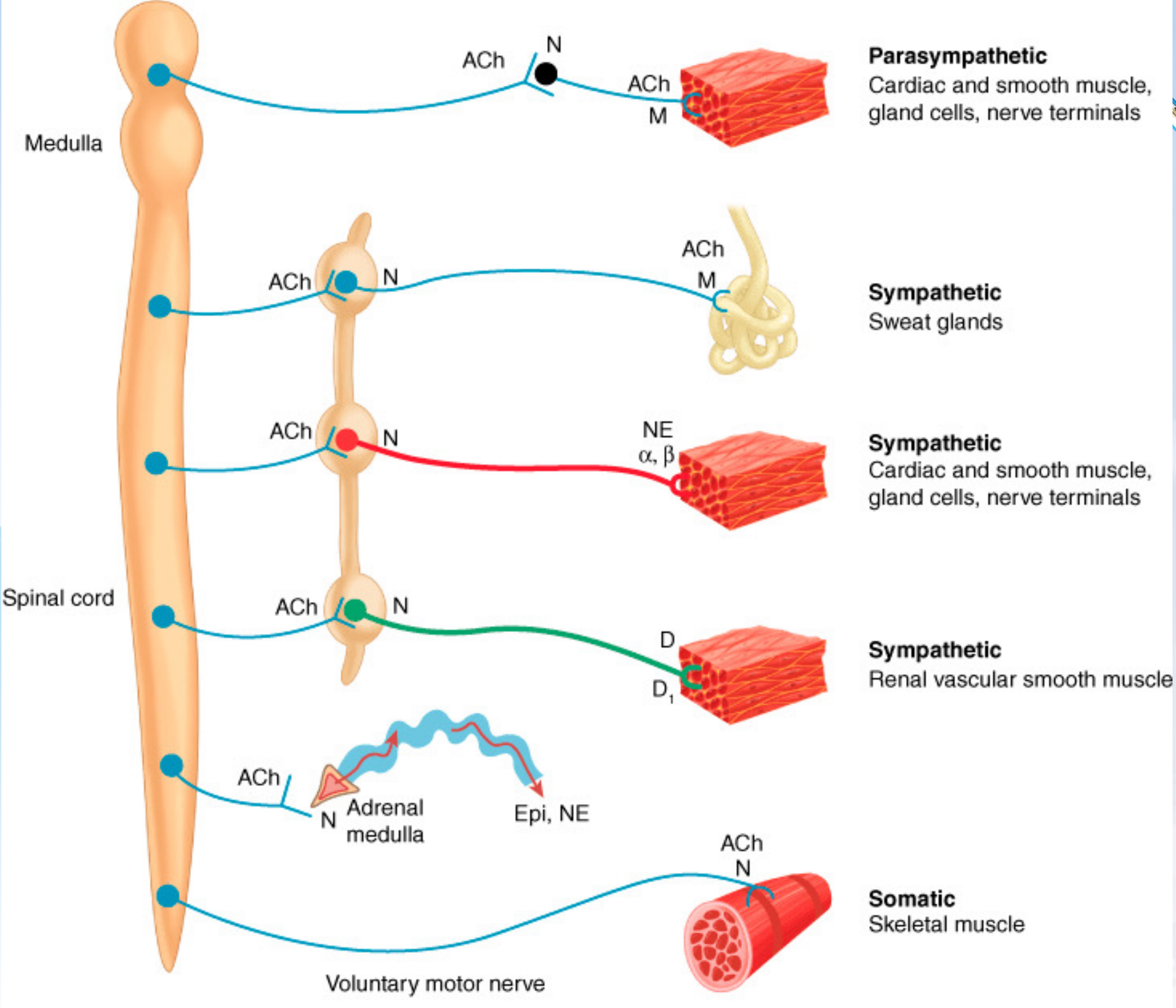
Chapter 6 Introduction to Autonomic Pharmacology

- The nervous system is conventionally divided into the
  - CNS: central nervous system
  - PNS: peripheral nervous system
    - The motor (efferent) portion of the nervous system can be divided into two major subdivisions: autonomic and somatic.
      - The **autonomic nervous system (ANS)** is largely independent (autonomous) in that its activities are not under direct conscious control. It is concerned primarily with visceral functions such as：
        - » cardiac output, blood flow to various organs, and digestion, which are necessary for life.
      - The **somatic** subdivision is largely concerned with consciously controlled functions such as movement, respiration, and posture.
    - Afferent (sensory)

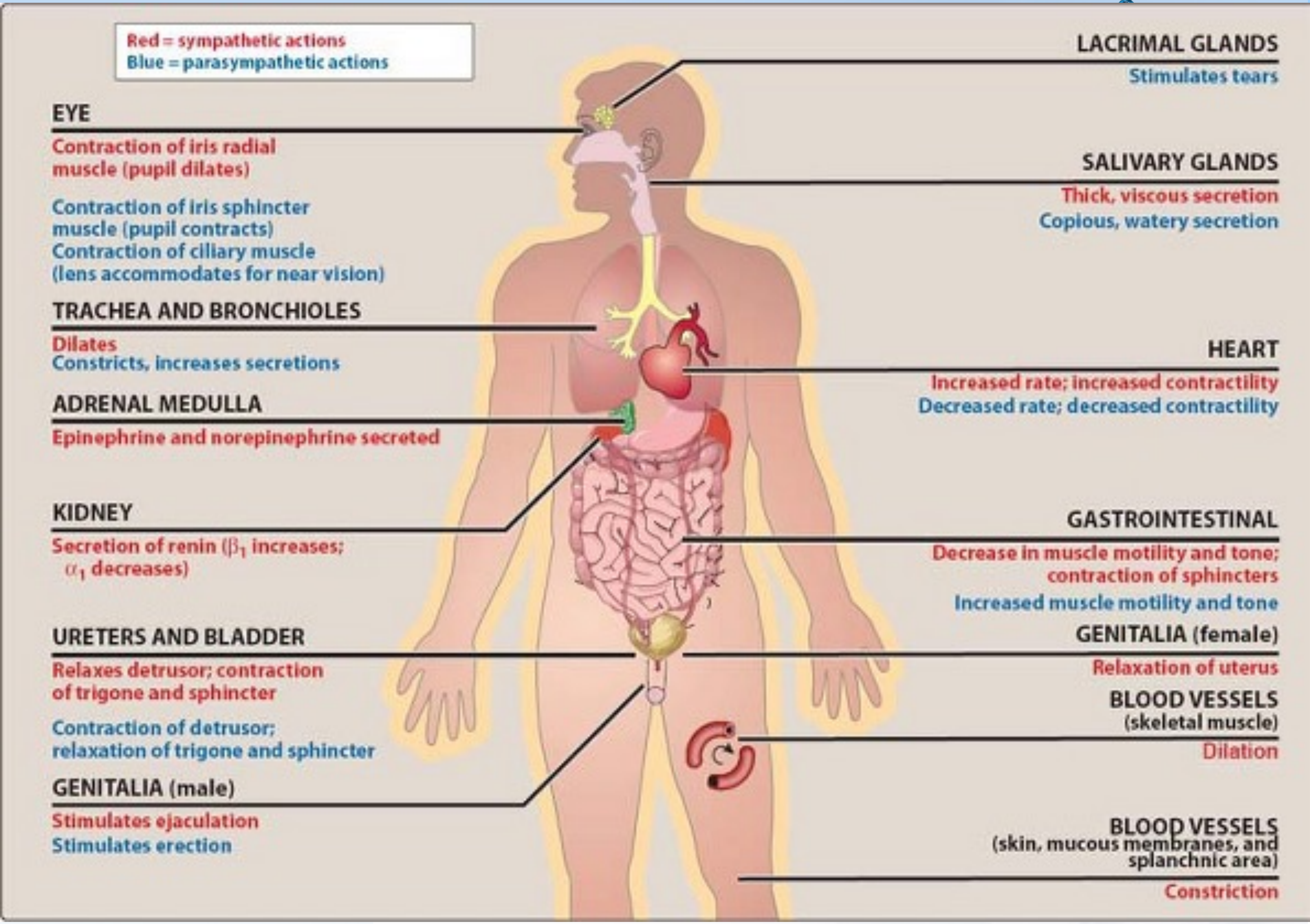


Anatomy of the Autonomic Nervous System

- The ANS lends itself to division on anatomic grounds into two major portions
  - the **sympathetic (thoracolumbar)** division
  - the **parasympathetic (craniosacral)** division
  - the enteric nervous system **(ENS)**



Medulla
Spinal cord
ACh
N
ACh
M
Parasympathetic
Cardiac and smooth muscle, gland cells, nerve terminals
ACh
N
ACh
M
Sympathetic
Sweat glands
ACh
N
NE
α, β
Sympathetic
Cardiac and smooth muscle, gland cells, nerve terminals
ACh
N
D
D1
Sympathetic
Renal vascular smooth muscle
ACh
N
Adrenal medulla
Epi, NE
ACh
N
Somatic
Skeletal muscle
Voluntary motor nerve

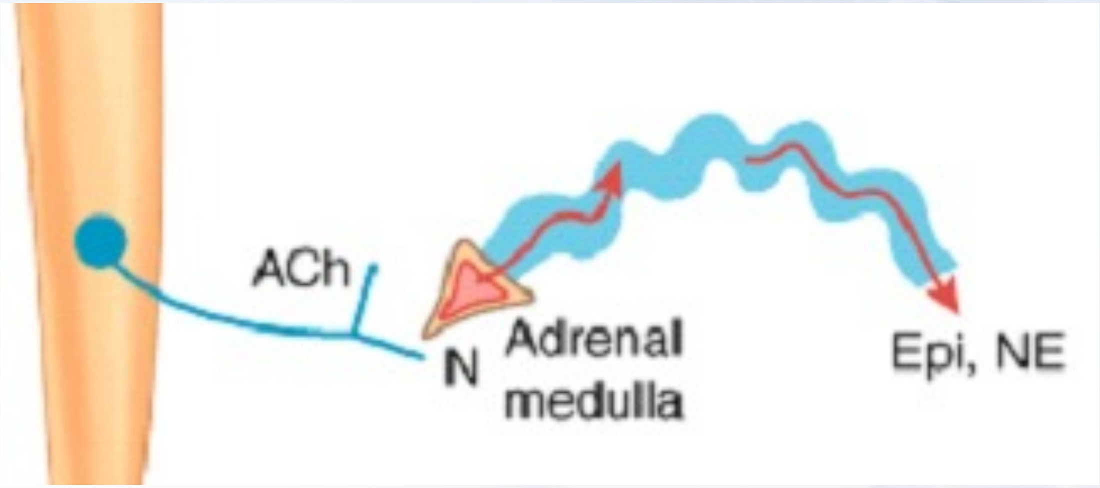


Red = sympathetic actions
Blue = parasympathetic actions
EYE
Contraction of iris radial muscle (pupil dilates)
Contraction of iris sphincter muscle (pupil contracts)
Contraction of ciliary muscle (lens accommodates for near vision)
TRACHEA AND BRONCHIOLES
Dilates
Constricts, increases secretions
ADRENAL MEDULLA
Epinephrine and norepinephrine secreted
KIDNEY
Secretion of renin (β1 increases; α1 decreases)
URETERS AND BLADDER
Relaxes detrusor; contraction of trigone and sphincter
Contraction of detrusor; relaxation of trigone and sphincter
GENITALIA (male)
Stimulates ejaculation
Stimulates erection
LACRIMAL GLANDS
Stimulates tears
SALIVARY GLANDS
Thick, viscous secretion
Copious, watery secretion
HEART
Increased rate; increased contractility
Decreased rate; decreased contractility
GASTROINTESTINAL
Decrease in muscle motility and tone; contraction of sphincters
Increased muscle motility and tone
GENITALIA (female)
Relaxation of uterus
BLOOD VESSELS (skeletal muscle)
Dilation
BLOOD VESSELS (skin, mucous membranes, and splanchnic area)
Constriction

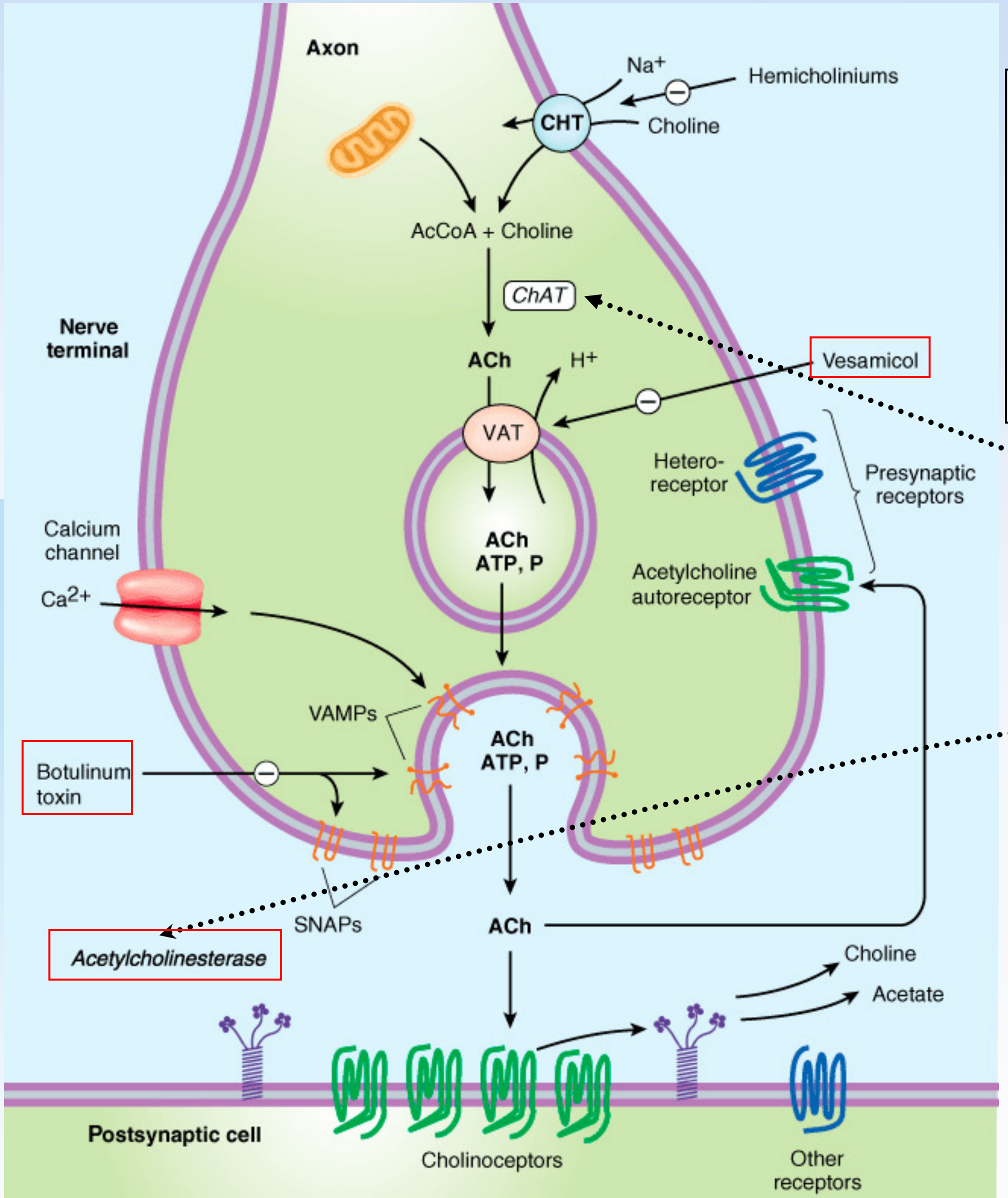
Neurotransmitter Chemistry of the Autonomic Nervous System

- acetylcholine or norepinephrine
  - An important traditional classification of autonomic nerves is based on the primary transmitter molecules
  - A large number of peripheral ANS fibers synthesize and release acetylcholine; they are <u>**cholinergic** fibers</u>; that is, they work by releasing acetylcholine
    - include all preganglionic efferent autonomic fibers and the somatic (nonautonomic) motor fibers to skeletal muscle

- Most postganglionic sympathetic fibers release norepinephrine (noradrenaline); they are **noradrenergic** (adrenergic) fibers
  - releasing norepinephrine
    - As noted, a few sympathetic fibers release acetylcholine



Cholinergic Transmission



sodium-dependent choline transporter (CHT)
choline acetyltransferase (ChAT).
vesicle-associated transporter (VAT)
synaptosomal nerve-associated proteins(SNAPs).
synaptosomal nerve-associated proteins (SNAPs).

Choline acetyltransferase inhibitors (-)

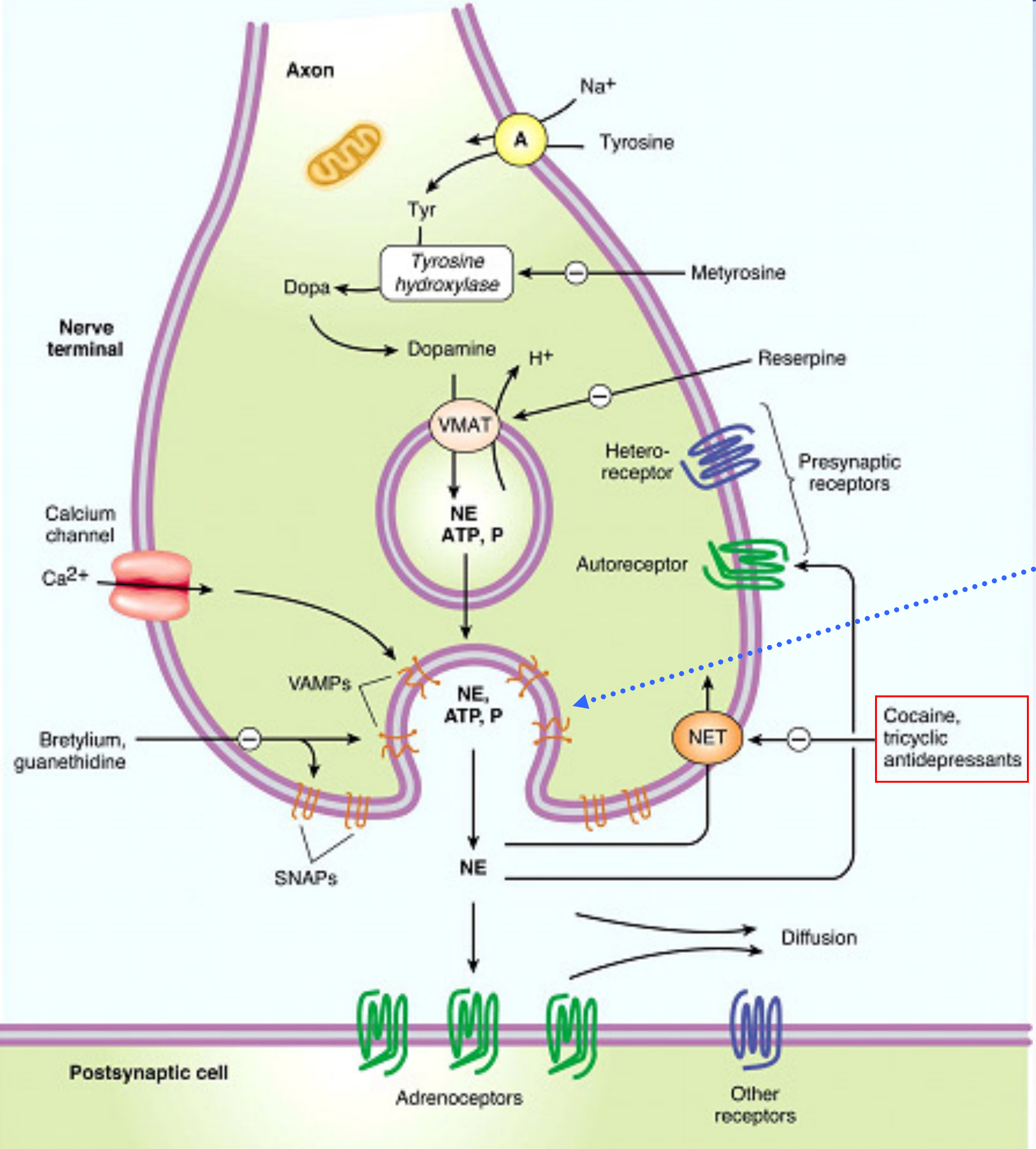
Acetylcholinesterase inhibitors:
Edrophonium, Neostigmine, Pyridostigmine

TABLE 6–1 Some of the transmitter substances found in autonomic nervous system (ANS), enteric nervous system (ENS), and nonadrenergic, noncholinergic neurons.[1]

Substance	Probable Roles
Acetylcholine (ACh)	The primary transmitter at ANS ganglia, at the somatic neuromuscular junction, and at parasympathetic postganglionic nerve endings. A primary excitatory transmitter to smooth muscle and secretory cells in the ENS. Probably also the major neuron-to-neuron ("ganglionic") transmitter in the ENS.
Adenosine triphosphate (ATP)	Acts as a transmitter or cotransmitter at many ANS-effector synapses.
Calcitonin gene-related peptide (CGRP)	Found with substance P in cardiovascular sensory nerve fibers. Present in some secretomotor ENS neurons and interneurons. A cardiac stimulant.
Cholecystokinin (CCK)	May act as a cotransmitter in some excitatory neuromuscular ENS neurons.
Dopamine	A modulatory transmitter in some ganglia and the ENS. Probably a postganglionic sympathetic transmitter in renal blood vessels.
Enkephalin and related opioid peptides	Present in some secretomotor and interneurons in the ENS. Appear to inhibit ACh release and thereby inhibit peristalsis. May *stimulate* secretion.
Galanin	Present in secretomotor neurons; may play a role in appetite-satiety mechanisms.
GABA (γ-aminobutyric acid)	May have presynaptic effects on excitatory ENS nerve terminals. Has some relaxant effect on the gut. Probably not a major transmitter in the ENS.
Gastrin-releasing peptide (GRP)	Extremely potent excitatory transmitter to gastrin cells. Also known as mammalian bombesin.
Neuropeptide Y (NPY)	Found in many noradrenergic neurons. Present in some secretomotor neurons in the ENS and may inhibit secretion of water and electrolytes by the gut. Causes long-lasting vasoconstriction. It is also a cotransmitter in some parasympathetic postganglionic neurons.
Nitric oxide (NO)	A cotransmitter at inhibitory ENS and other neuromuscular junctions; may be especially important at sphincters. Synthesized on demand by nitric oxide synthase (NOS), not stored; see Chapter 19.
Norepinephrine (NE)	The primary transmitter at most sympathetic postganglionic nerve endings.
Serotonin (5-HT)	An important transmitter or cotransmitter at excitatory neuron-to-neuron junctions in the ENS.
Substance P (related tachykinins)	Substance P is an important sensory neuron transmitter in the ENS and elsewhere. Tachykinins appear to be excitatory cotransmitters with ACh at ENS neuromuscular junctions. Found with CGRP in cardiovascular sensory neurons. Substance P is a vasodilator (probably via release of nitric oxide).
Vasoactive intestinal peptide (VIP)	Excitatory secretomotor transmitter in the ENS; may also be an inhibitory ENS neuromuscular cotransmitter. A probable cotransmitter in many cholinergic neurons. A vasodilator (found in many perivascular neurons) and cardiac stimulant.

[1]See Chapter 21 for transmitters found in the central nervous system.

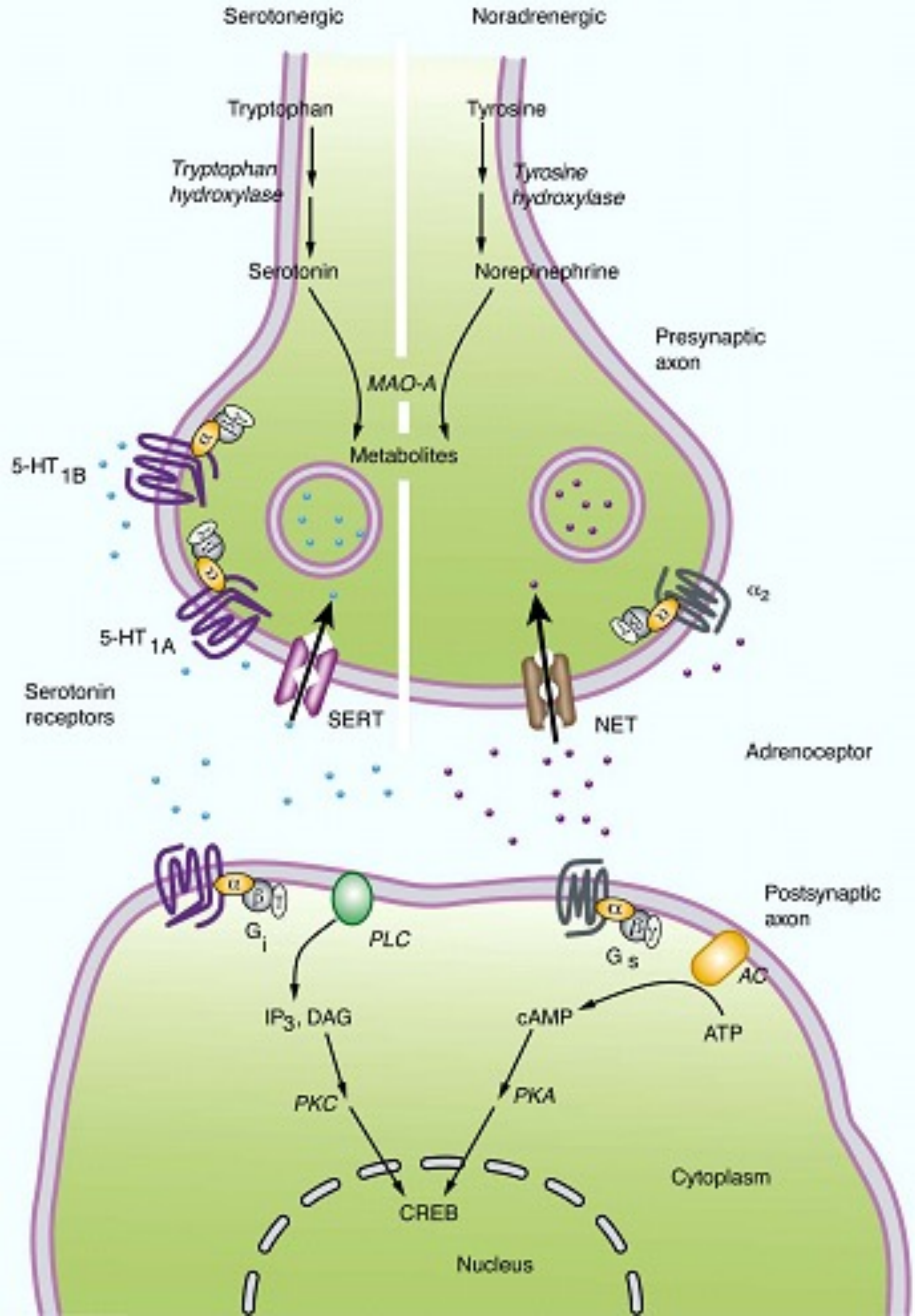
Adrenergic Transmission



vesicular monoamine transporter (VMAT)

norepinephrine transporter (NET)

(+) **tyramine,amphetamines,** and **ephedrine**



Monoamine oxidase (MAO)

MAO_A主要代謝EPi, NE，5-HT

MAO_B主要代謝dopamin、tyramine

MAO_AI: Moclobemide

MAO_BI: Selegiline

$MAO_AI + MAO_BI$

Phenelzine

Tranylcypromine

Isocarboxazide

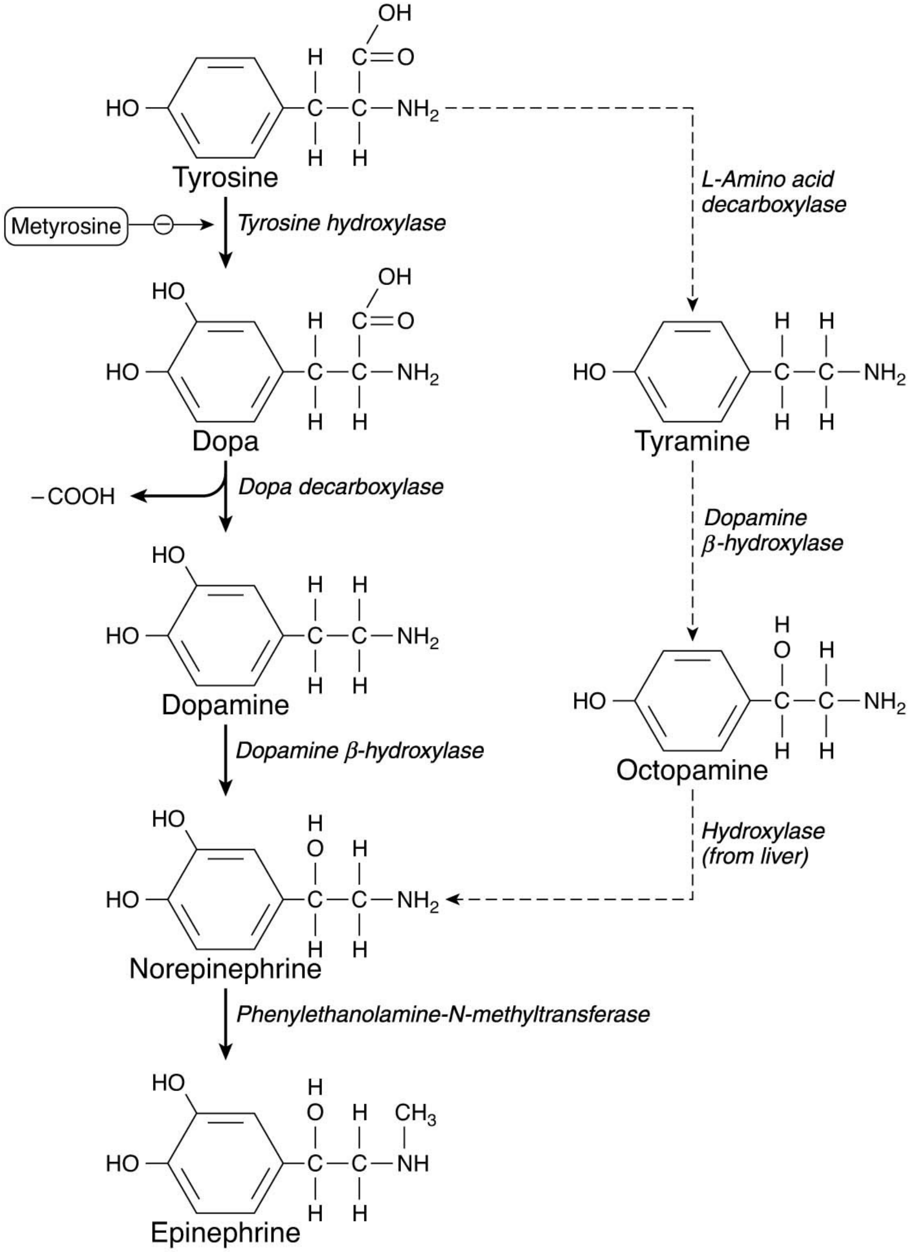


FIGURE 6–5 Biosynthesis of catecholamines. The rate-limiting step, conversion of tyrosine to dopa, can be inhibited by metyrosine (α-methyltyrosine). The alternative pathway shown by the dashed arrows has not been found to be of physiologic significance in humans. However, tyramine and octopamine may accumulate in patients treated with monoamine oxidase inhibitors. (Reproduced, with permission, from Greenspan FS, Gardner DG [editors]: *Basic and Clinical Endocrinology*, 7th ed. McGraw-Hill, 2003.)

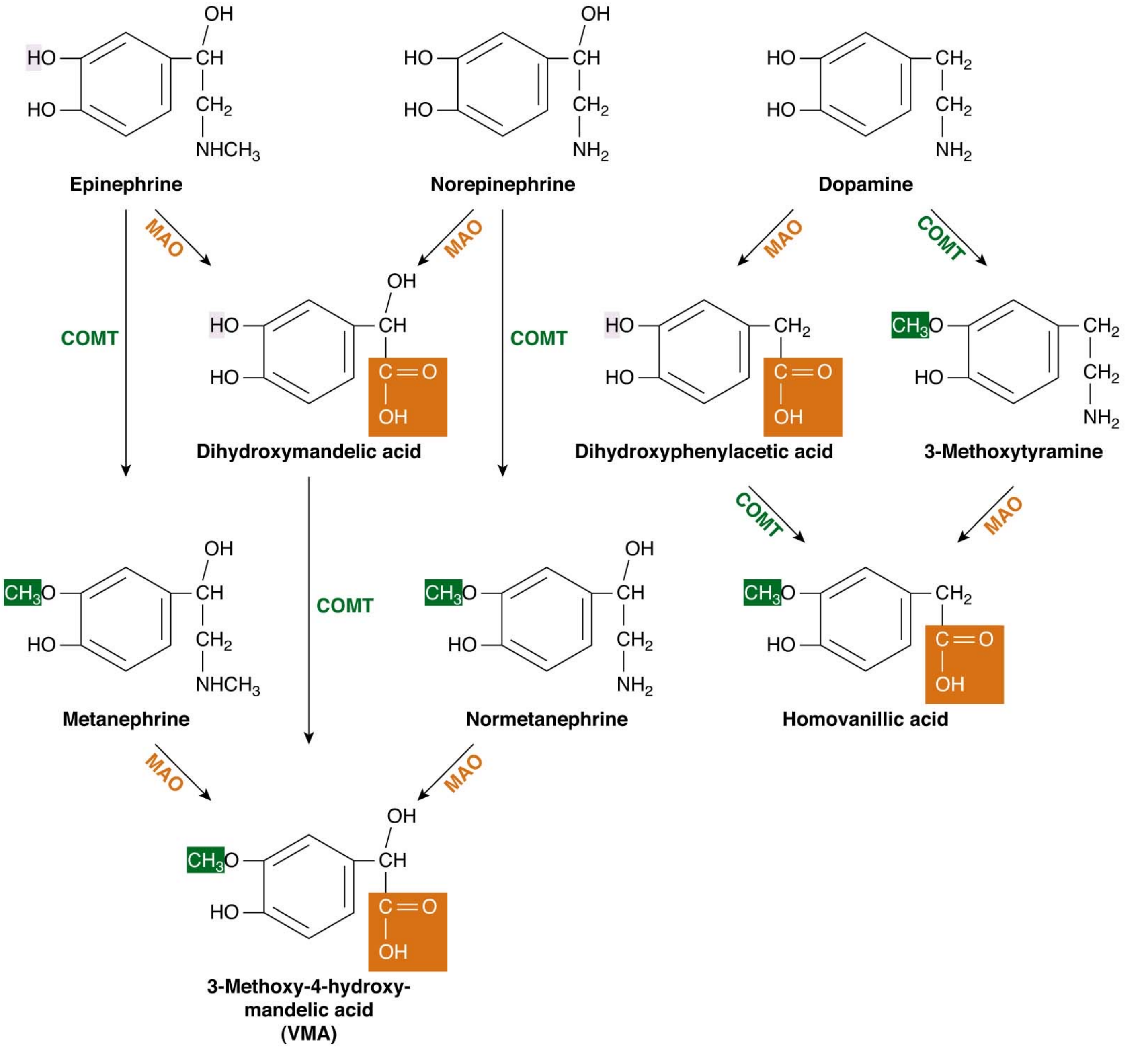


FIGURE 6–6 Metabolism of catecholamines by catechol-*O*-methyltransferase (COMT) and monoamine oxidase (MAO). (Modified and reproduced, with permission, from Greenspan FS, Gardner DG [editors]: *Basic and Clinical Endocrinology*, 7th ed. McGraw-Hill, 2003.)

Autonomic Receptors

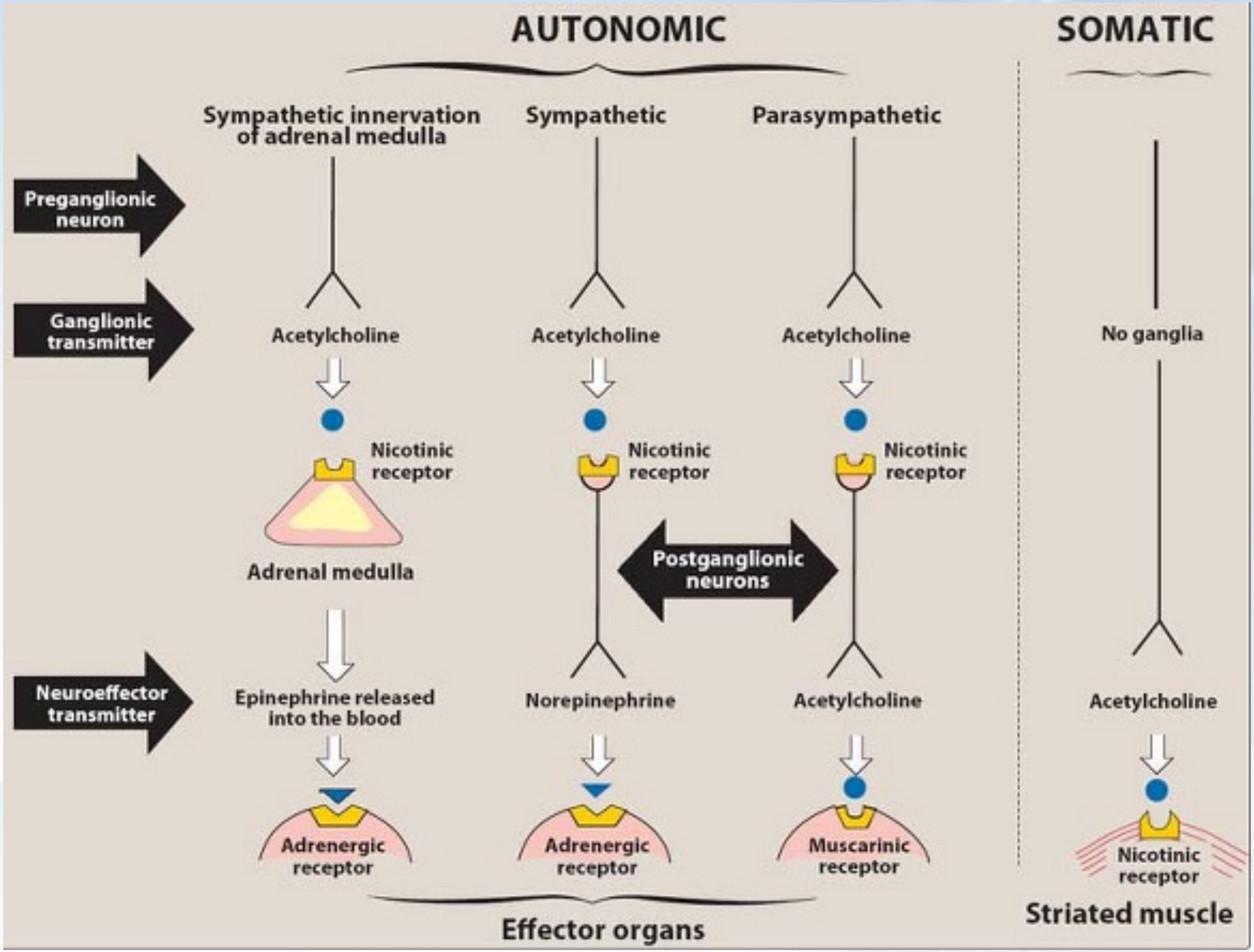


TABLE 6–2 Major autonomic receptor types.

Receptor Name	Typical Locations	Result of Ligand Binding
Cholinoceptors		
Muscarinic M_1	CNS neurons, sympathetic postganglionic neurons, some presynaptic sites	Formation of IP_3 and DAG, increased intracellular calcium
Muscarinic M_2	Myocardium, smooth muscle, some presynaptic sites; CNS neurons	Opening of potassium channels, inhibition of adenylyl cyclase
Muscarinic M_3	Exocrine glands, vessels (smooth muscle and endothelium); CNS neurons	Like M_1 receptor-ligand binding
Muscarinic M_4	CNS neurons; possibly vagal nerve endings	Like M_2 receptor-ligand binding
Muscarinic M_5	Vascular endothelium, especially cerebral vessels; CNS neurons	Like M_1 receptor-ligand binding
Nicotinic N_N	Postganglionic neurons, some presynaptic cholinergic terminals	Opening of Na^+,K^+ channels, depolarization
Nicotinic N_M	Skeletal muscle neuromuscular end plates	Opening of Na^+,K^+ channels, depolarization
Adrenoceptors		
$Alpha_1$	Postsynaptic effector cells, especially smooth muscle	Formation of IP_3 and DAG, increased intracellular calcium
$Alpha_2$	Presynaptic adrenergic nerve terminals, platelets, lipocytes, smooth muscle	Inhibition of adenylyl cyclase, decreased cAMP
$Beta_1$	Postsynaptic effector cells, especially heart, lipocytes, brain; presynaptic adrenergic and cholinergic nerve terminals, juxtaglomerular apparatus of renal tubules, ciliary body epithelium	Stimulation of adenylyl cyclase, increased cAMP
$Beta_2$	Postsynaptic effector cells, especially smooth muscle and cardiac muscle	Stimulation of adenylyl cyclase and increased cAMP. Activates cardiac G_i under some conditions.
$Beta_3$	Postsynaptic effector cells, especially lipocytes; heart	Stimulation of adenylyl cyclase and increased cAMP[1]
Dopamine receptors		
D_1 (DA_1), D_5	Brain; effector tissues, especially smooth muscle of the renal vascular bed	Stimulation of adenylyl cyclase and increased cAMP
D_2 (DA_2)	Brain; effector tissues, especially smooth muscle; presynaptic nerve terminals	Inhibition of adenylyl cyclase; increased potassium conductance D_3
D_3	Brain	Inhibition of adenylyl cyclase D_4
D_4	Brain, cardiovascular system	Inhibition of adenylyl cyclase

Functional Organization of Autonomic Activity

- Autonomic function is integrated and regulated at many levels, from the CNS to the effector cells.
- Most regulation uses negative feedback, but several other mechanisms have been identified. Negative feedback is particularly important in the responses of the ANS to the administration of autonomic drugs

Central Integration

- ANS and the endocrine system are integrated with each other
  - interactions are such that early investigators called
    - the parasympathetic system a **trophotropic** (趨養性)one (ie, leading to growth) used to "rest and digest"
    - the sympathetic system an **ergotropic** (增強抵抗力;強化作用)one (ie, leading to energy expenditure), which is activated for "fight or flight."

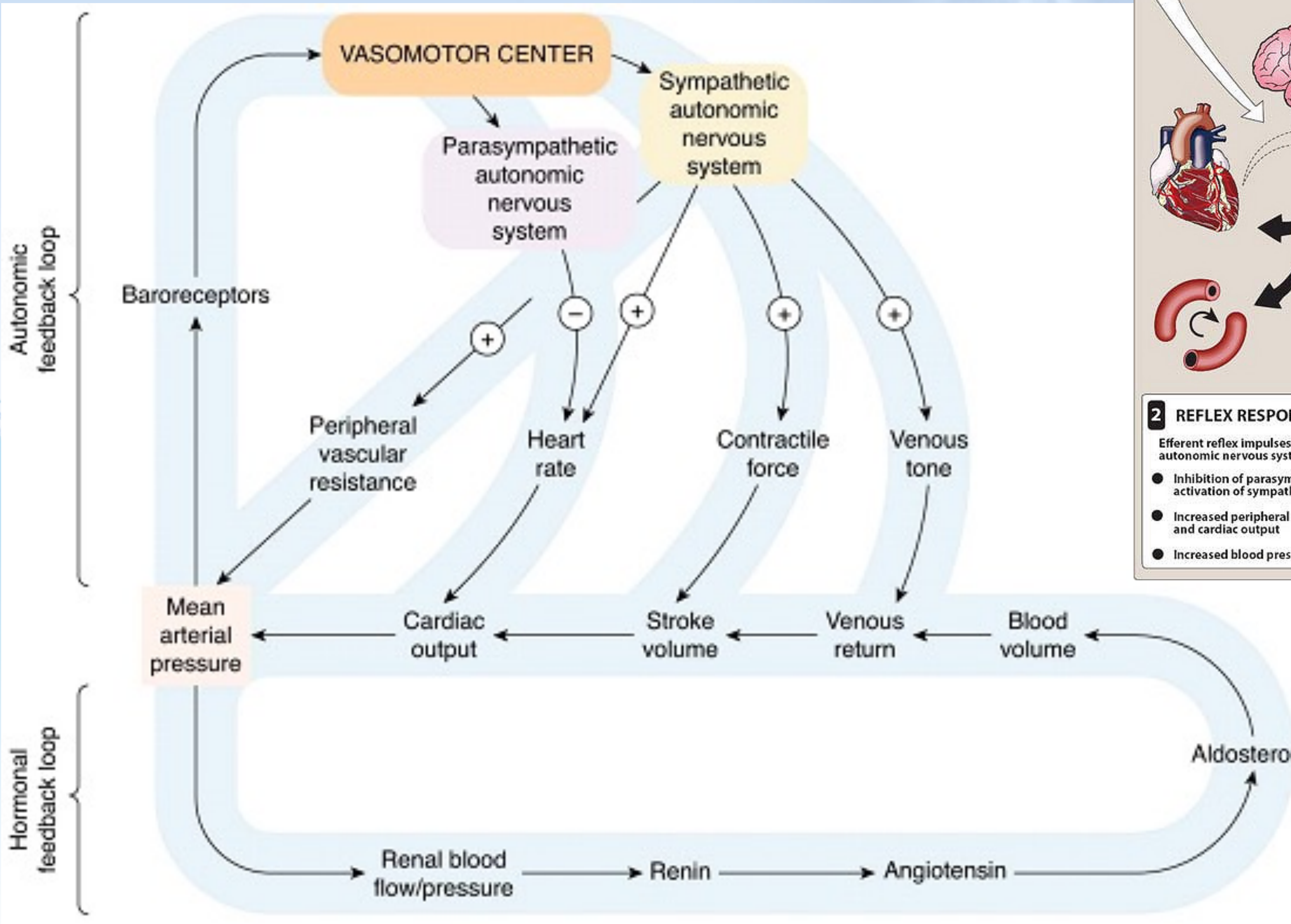
TABLE 6–3 **Direct effects of autonomic *nerve* activity on some organ systems. Autonomic *drug* effects are similar but not identical (see text).**

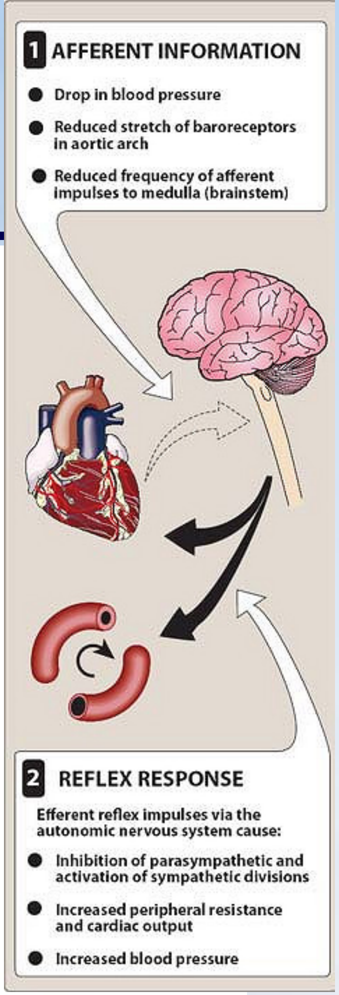
	Effect of			
	Sympathetic Activity		Parasympathetic Activity	
Organ	*Action*[1]	*Receptor*[2]	*Action*	*Receptor*[2]
Eye				
Iris radial muscle	Contracts	α_1	...	...
Iris circular muscle	...	...	Contracts	M_3
Ciliary muscle	[Relaxes]	β	Contracts	M_3
Heart				
Sinoatrial node	Accelerates	β_1, β_2	Decelerates	M_2
Ectopic pacemakers	Accelerates	β_1, β_2	...	...
Contractility	Increases	β_1, β_2	Decreases (atria)	M_2
Blood vessels				
Skin, splanchnic vessels	Contracts	α	...	...
Skeletal muscle vessels	Relaxes	β_2	...	...
	[Contracts]	α	...	...
	Relaxes[3]	M[3]	...	...
Endothelium (drug effect)			Releases EDRF[4]	M_3, M_5[5]
Bronchiolar smooth muscle	Relaxes	β_2	Contracts	M_3
Gastrointestinal tract				
Smooth muscle				
Walls	Relaxes	α_2,[6] β_2	Contracts	M_3
Sphincters	Contracts	α_1	Relaxes	M_3
Secretion	...	...	Increases	M_3
Genitourinary smooth muscle				
Bladder wall	Relaxes	β_2	Contracts	M_3
Sphincter	Contracts	α_1	Relaxes	M_3
Uterus, pregnant	Relaxes	β_2	...	...
	Contracts	α	Contracts	M_3
Penis, seminal vesicles	Ejaculation	α	Erection	M

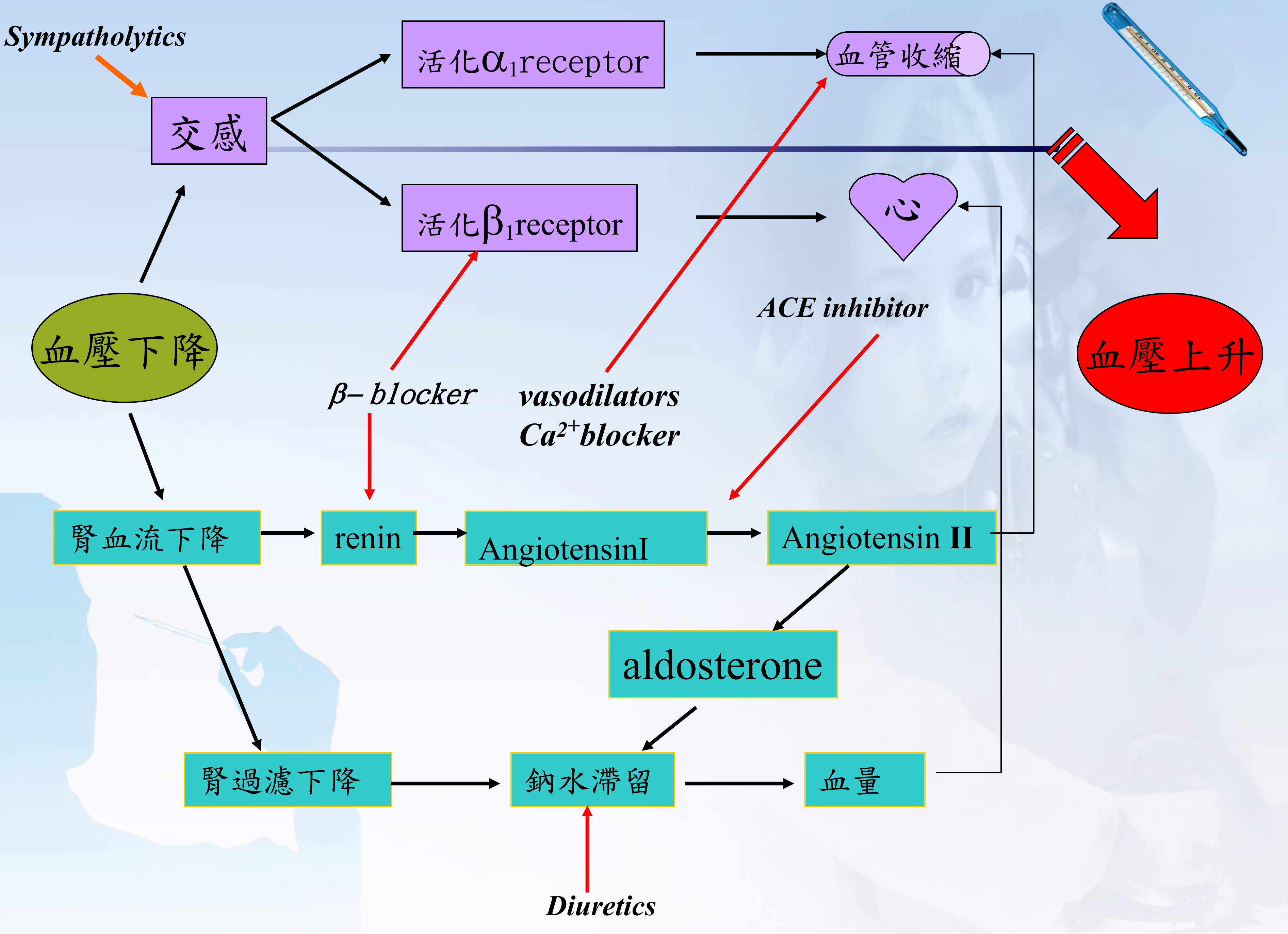
TABLE 6–3 **Direct effects of autonomic *nerve* activity on some organ systems. Autonomic *drug* effects are similar but not identical (see text). (Continued)**

	Effect of			
	Sympathetic Activity		Parasympathetic Activity	
Organ	*Action*[1]	*Receptor*[2]	*Action*	*Receptor*[2]
Skin				
Pilomotor smooth muscle	Contracts	α	...	...
Sweat glands			...	...
Eccrine	Increases	M	...	...
Apocrine (stress)	Increases	α	...	...
Metabolic functions				
Liver	Gluconeogenesis	β_2, α	...	...
Liver	Glycogenolysis	β_2, α	...	...
Fat cells	Lipolysis	β_3	...	...
Kidney	Renin release	β_1	...	...

Integration of Cardiovascular Function







Sympatholytics
交感
活化α1receptor
活化β1receptor
血管收縮
心
血壓上升
血壓下降
β– blocker
vasodilators
Ca2+blocker
ACE inhibitor
腎血流下降
renin
AngiotensinI
Angiotensin II
aldosterone
腎過濾下降
鈉水滯留
血量
Diuretics

Presynaptic Regulation

- Presynaptic receptors that respond to the primary transmitter substance released by the nerve ending are called **autoreceptors.**
  - Autoreceptors are usually inhibitory, but in addition to the excitatory receptors on noradrenergic fibers, many cholinergic fibers, especially somatic motor fibers, have excitatory nicotinic autoreceptors.

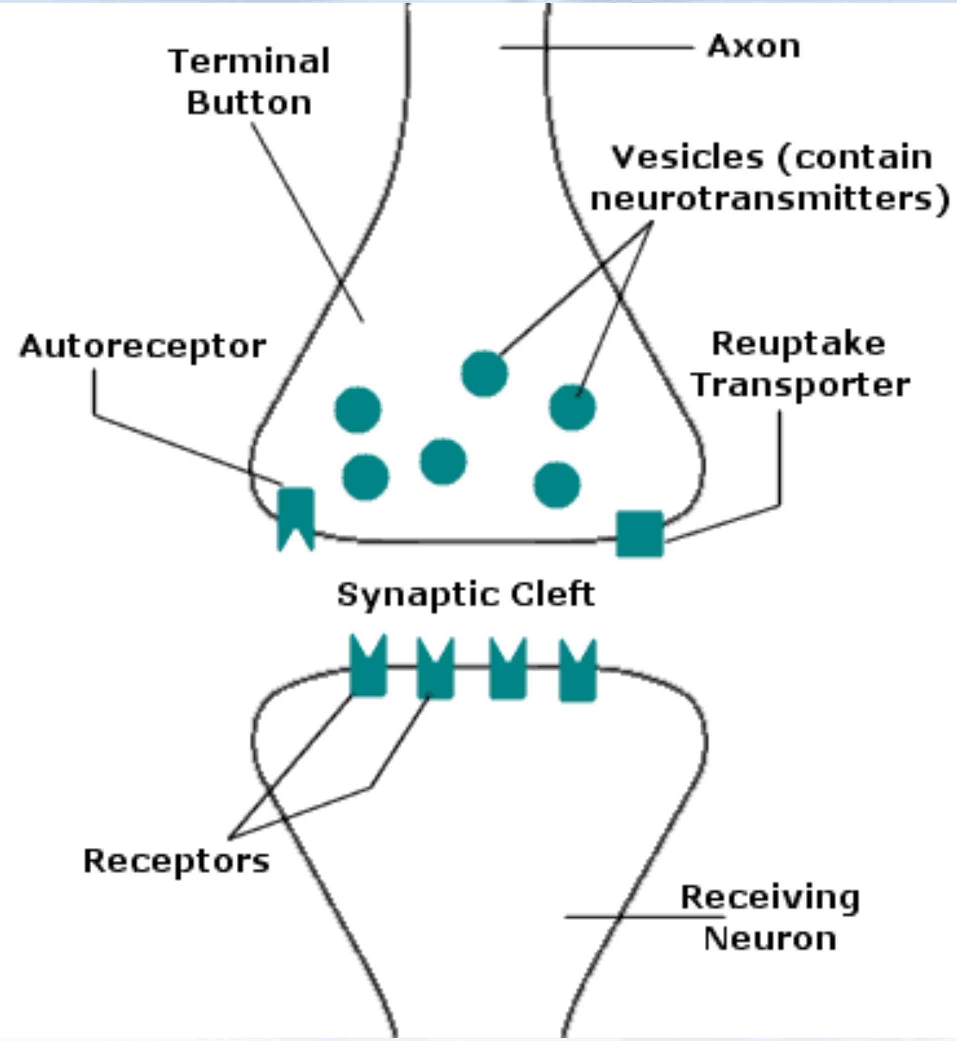
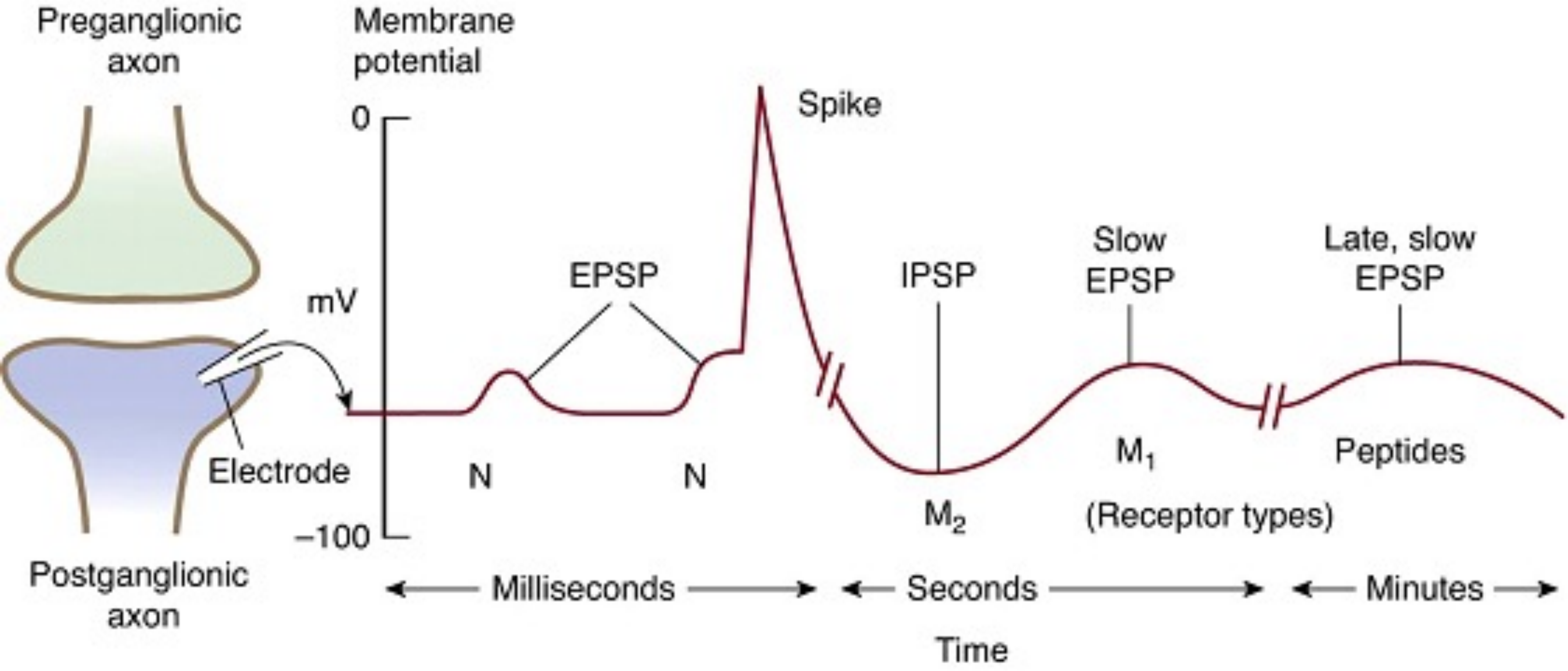


TABLE 6–4 Autoreceptor, heteroreceptor, and modulatory effects in peripheral synapses.[1]

Transmitter/Modulator	Receptor Type	Neuron Terminals Where Found
Inhibitory effects		
Acetylcholine	M_2, M_1	Adrenergic, enteric nervous system
Norepinephrine	$Alpha_2$	Adrenergic clonidine
Dopamine	D_2; less evidence for D_1	Adrenergic
Serotonin (5-HT)	$5\text{-}HT_1$, $5\text{-}HT_2$, $5\text{-}HT_3$	Cholinergic preganglionic
ATP and adenosine	P_2 (ATP), P_1 (adenosine)	Adrenergic autonomic and ENS cholinergic neurons
Histamine	H_3, possibly H_2	H_3 type identified on CNS adrenergic and serotonergic neurons
Enkephalin	Delta (also mu, kappa)	Adrenergic, ENS cholinergic
Neuropeptide Y	Y_1, Y_2 (NPY)	Adrenergic, some cholinergic
Prostaglandin E_1, E_2	EP_3	Adrenergic
Excitatory effects		
Epinephrine	$Beta_2$	Adrenergic, somatic motor cholinergic
Acetylcholine	NM	Somatic motor cholinergic
Angiotensin II	AT_1	Adrenergic

[1] A provisional list. The number of transmitters and locations will undoubtedly increase with additional research.

Postsynaptic Regulation



Pharmacology of the Eye

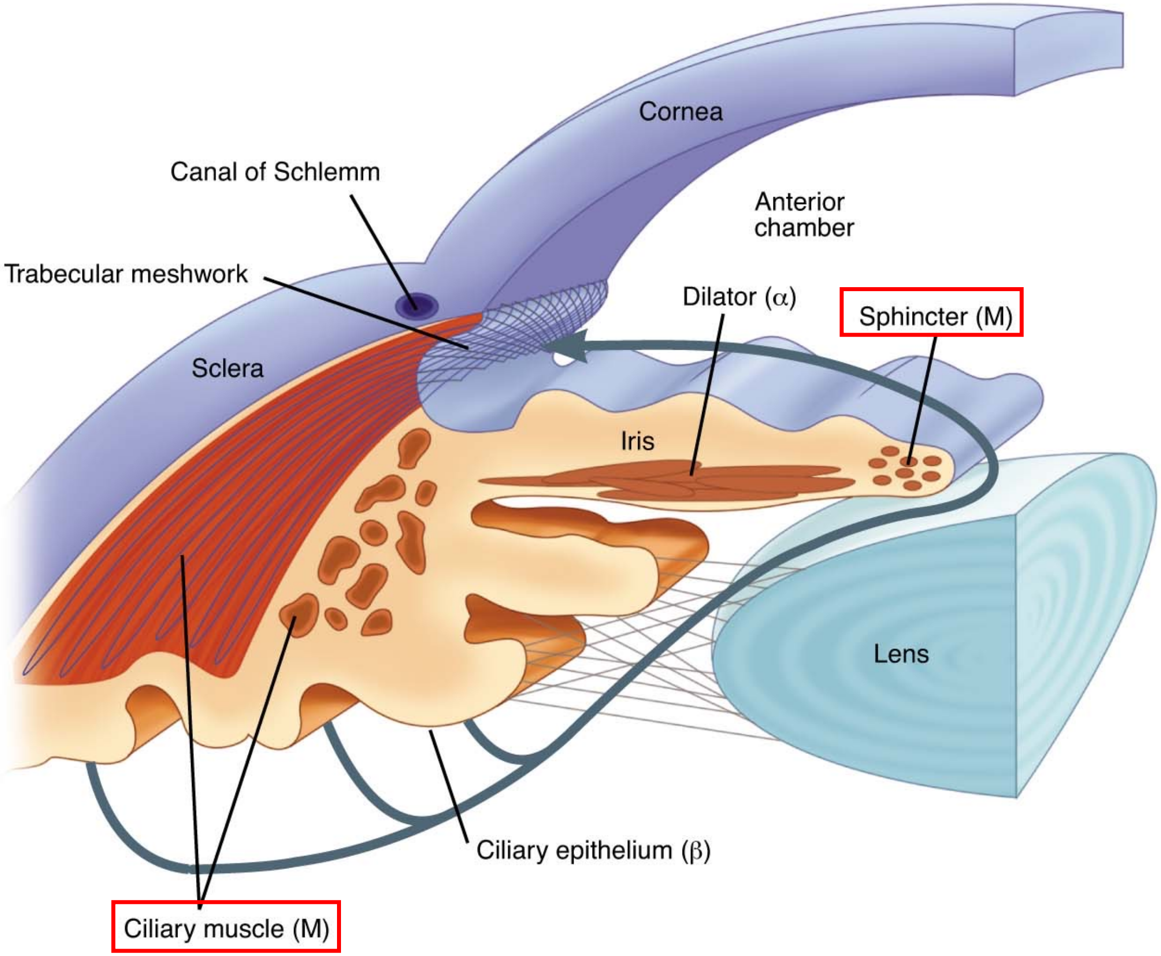
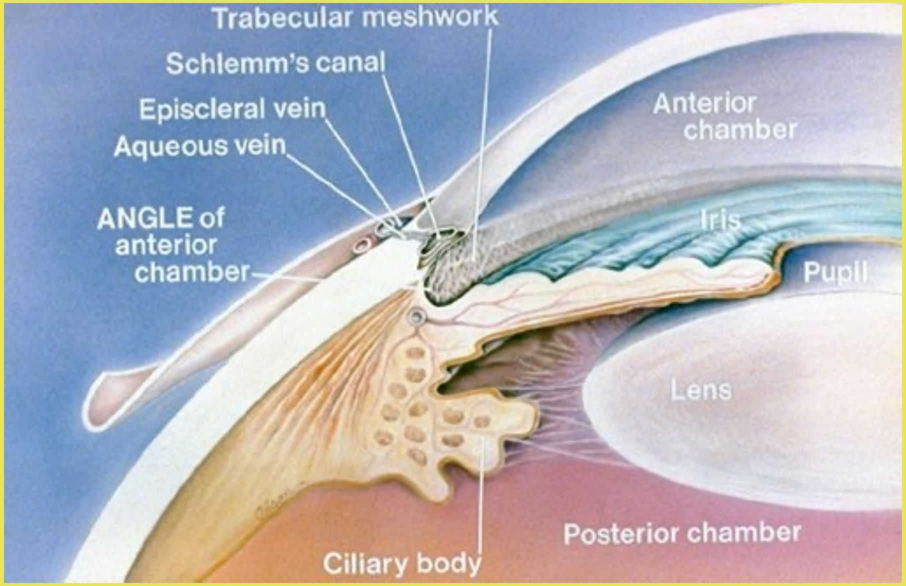


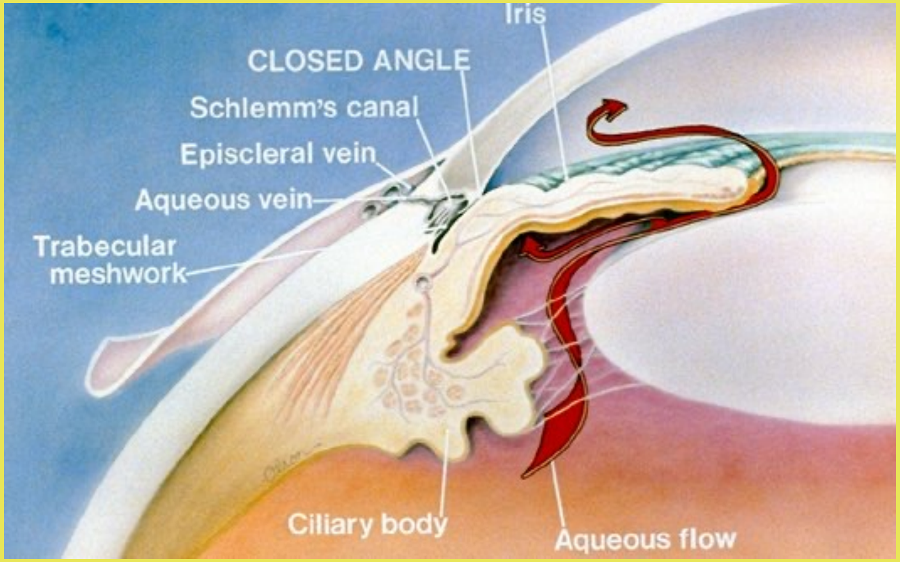
FIGURE 6–9 Structures of the anterior chamber of the eye. Tissues with significant autonomic functions and the associated ANS receptors are shown in this schematic diagram. Aqueous humor is secreted by the epithelium of the ciliary body, flows into the space in front of the iris, flows through the trabecular meshwork, and exits via the canal of Schlemm (*arrow*). Blockade of the β adrenoceptors associated with the ciliary epithelium causes decreased secretion of aqueous. Blood vessels (not shown) in the sclera are also under autonomic control and influence aqueous drainage.

開放型



Trabecular meshwork
Schlemm's canal
Episcleral vein
Aqueous vein
ANGLE of anterior chamber
Anterior chamber
Iris
Pupil
Lens
Posterior chamber
Ciliary body

閉鎖性

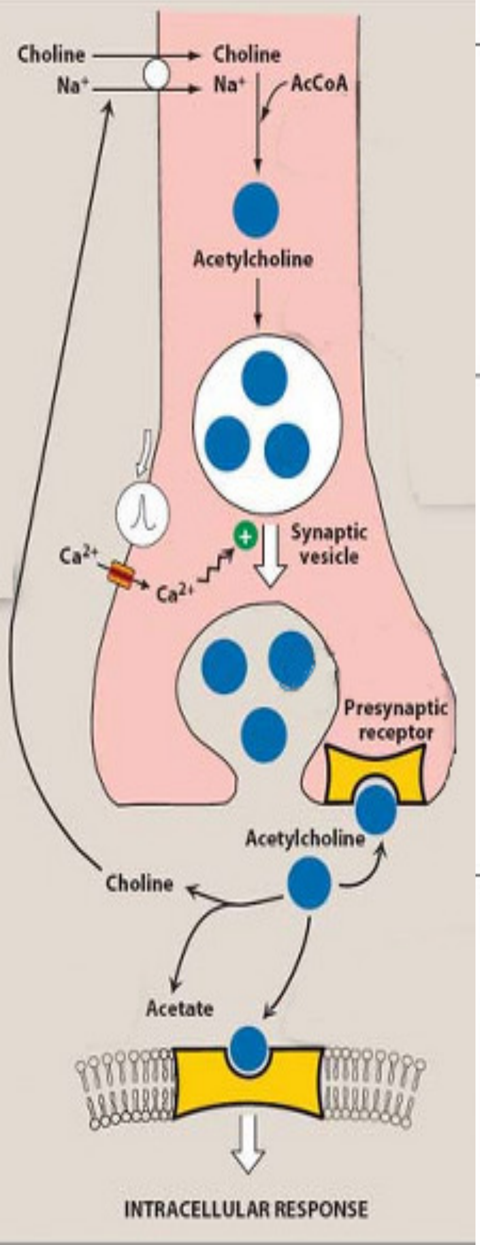


Iris
CLOSED ANGLE
Schlemm's canal
Episcleral vein
Aqueous vein
Trabecular meshwork
Ciliary body
Aqueous flow

Chapter 7

Cholinoceptor-Activating & Cholinesterase-Inhibiting Drugs

Overview



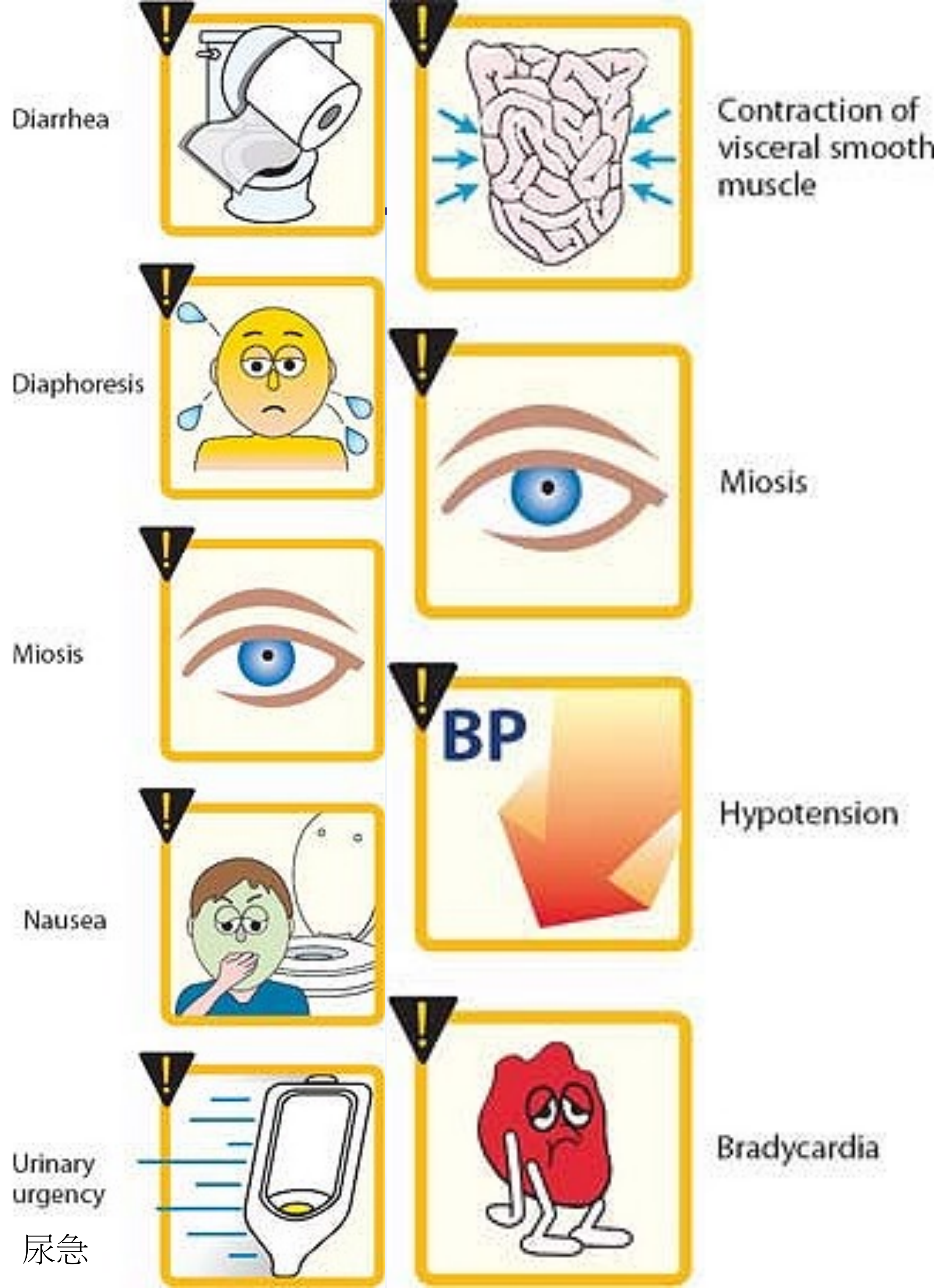
CHOLINERGIC AGONISTS

DIRECT ACTING
- *Acetylcholine*
- *Bethanechol*
- *Carbachol*
- *Cevimeline*
- *Pilocarpine*

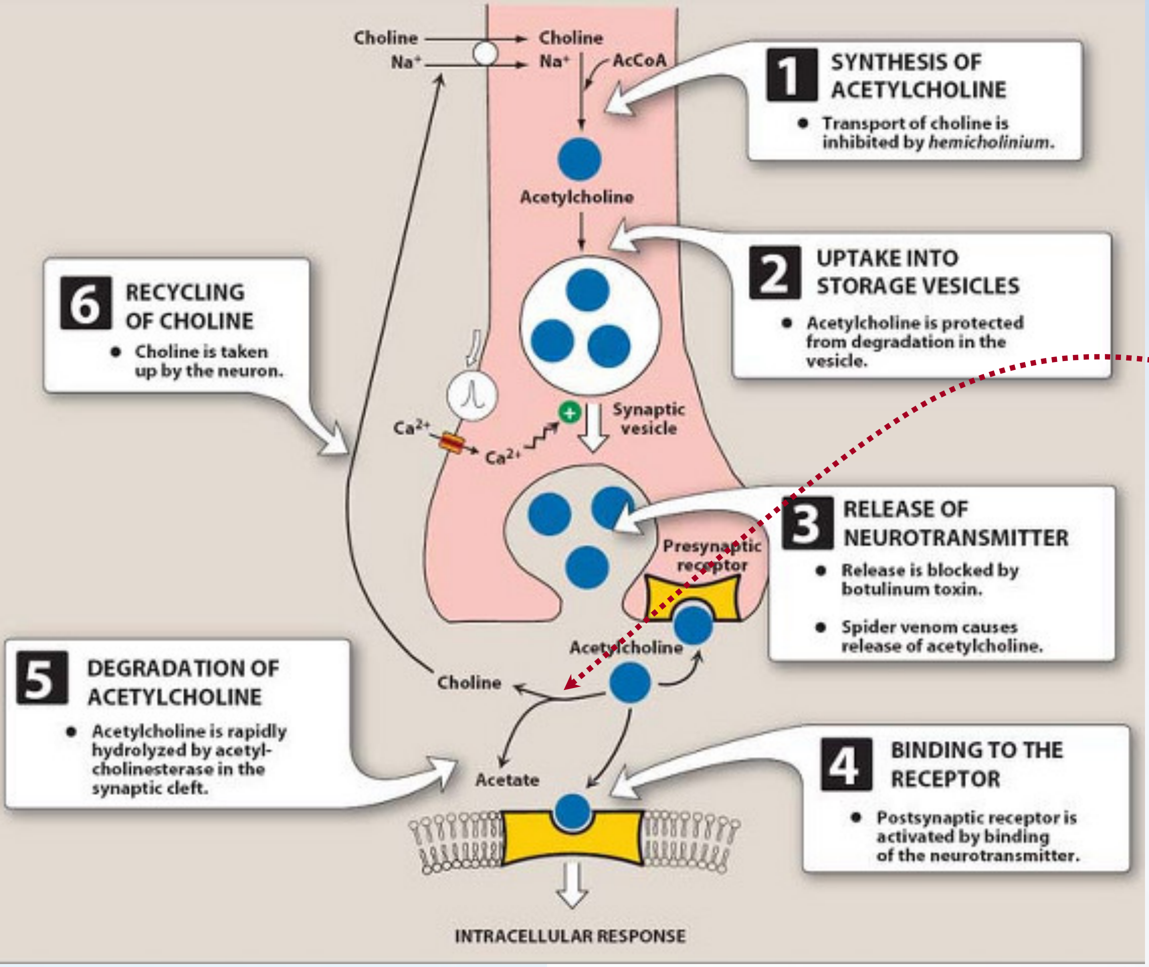
INDIRECT ACTING (reversible)
- *Ambenomium*
- *Demecarium*
- *Donezepil*
- *Edrophonium*
- *Galantamine*
- *Neostigmine*
- *Physostigmine*
- *Pyridostigmine*
- *Rivastigmine*
- *Tacrine*

INDIRECT ACTING (irreversible)
- *Echothiophate*

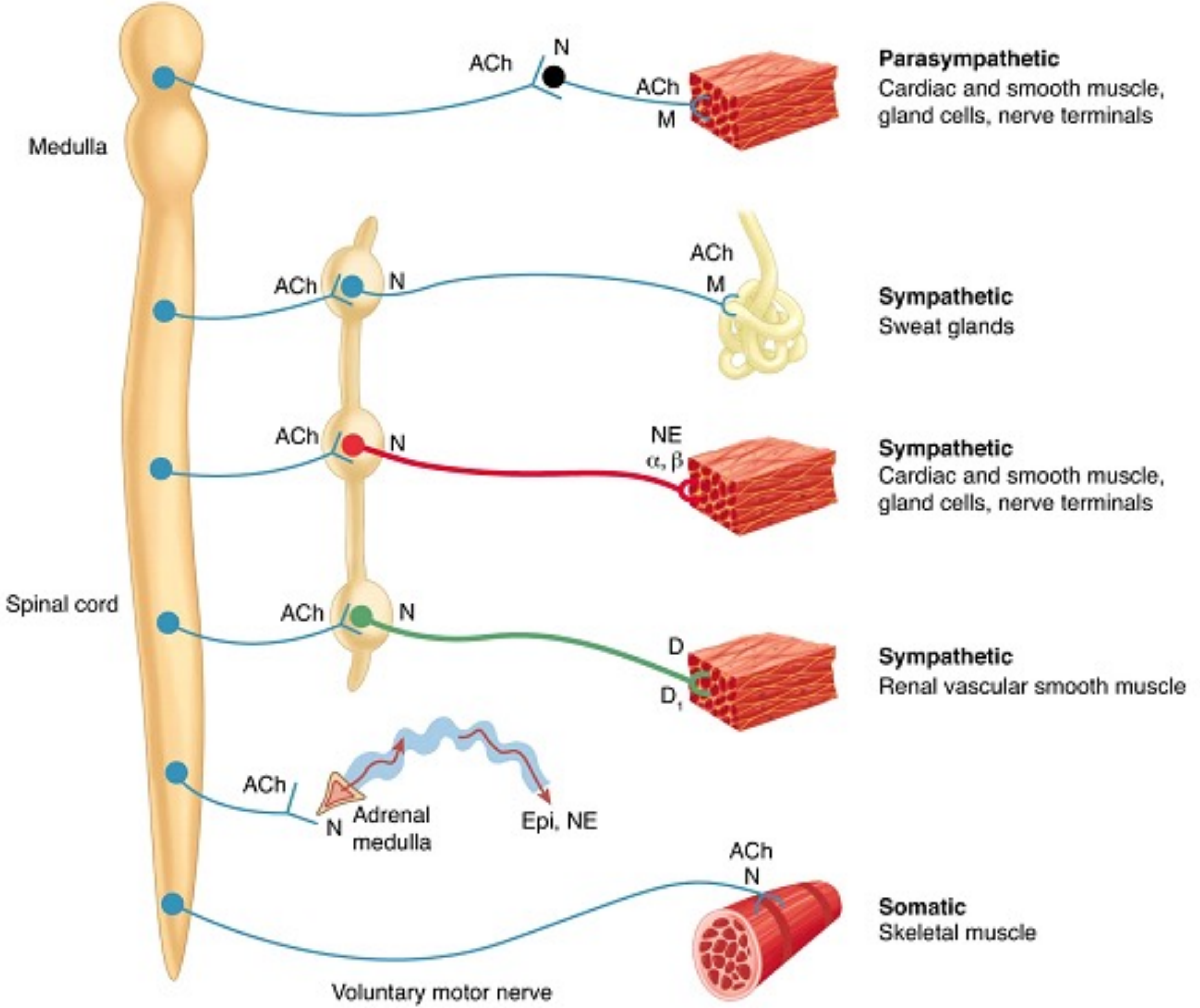
REACTIVATION OF ACETYLCHOLINE ESTERASE
- *Pralidoxime*



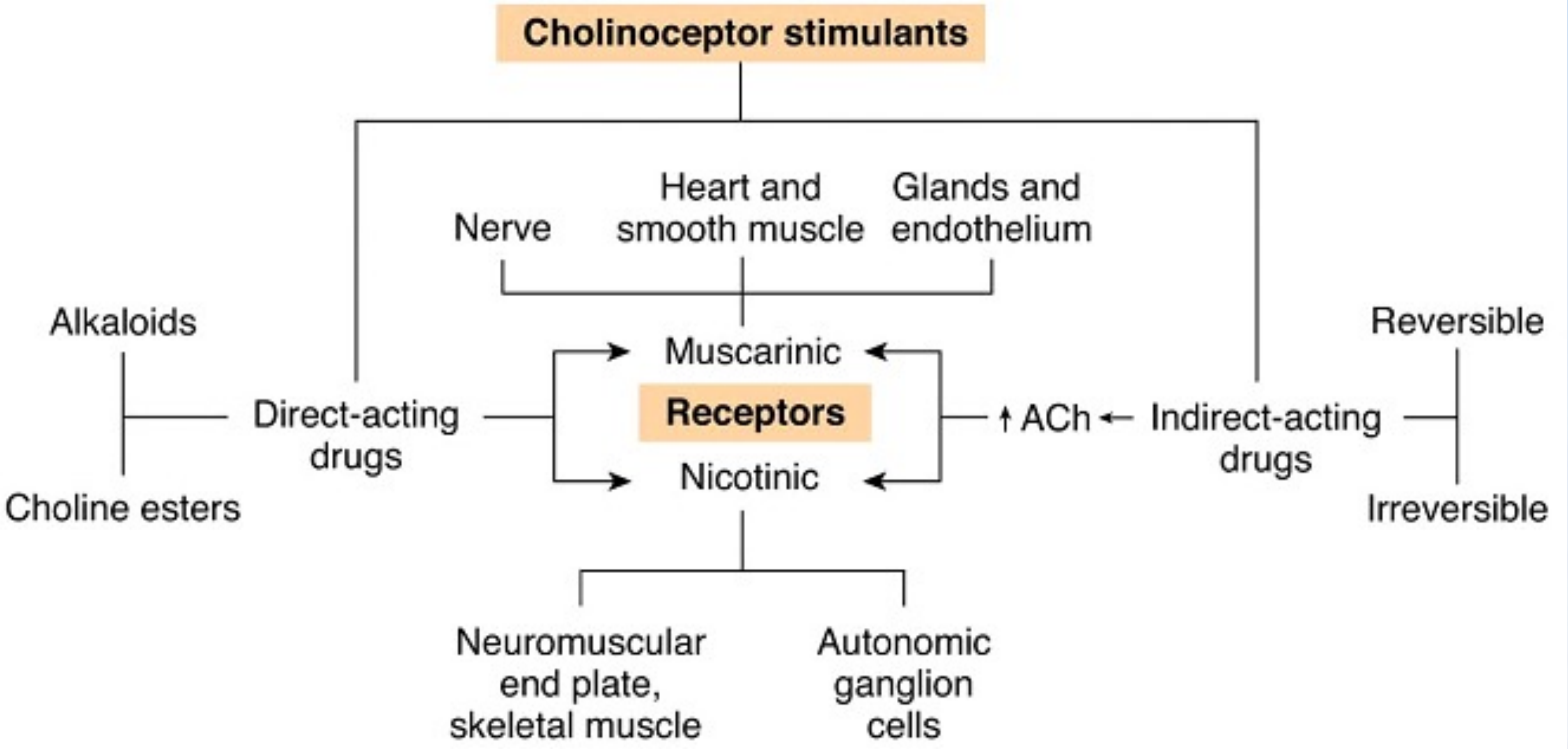
Introduction



- Acetylcholine-receptor stimulants and cholinesterase inhibitors together make up a large group of drugs that mimic acetylcholine (cholinomimetic agents)



Medulla
ACh
N
ACh
M
Parasympathetic
Cardiac and smooth muscle, gland cells, nerve terminals
ACh
N
ACh
M
Sympathetic
Sweat glands
ACh
N
NE
α, β
Sympathetic
Cardiac and smooth muscle, gland cells, nerve terminals
Spinal cord
ACh
N
D
D1
Sympathetic
Renal vascular smooth muscle
ACh
N
Adrenal medulla
Epi, NE
ACh
N
Somatic
Skeletal muscle
Voluntary motor nerve



Cholinoceptor stimulants
Heart and smooth muscle
Glands and endothelium
Nerve
Alkaloids
Reversible
Muscarinic
Receptors
Direct-acting drugs
↑ ACh
Indirect-acting drugs
Nicotinic
Choline esters
Irreversible
Neuromuscular end plate, skeletal muscle
Autonomic ganglion cells

TABLE 7–1 Subtypes and characteristics of cholinoceptors.

Receptor Type	Other Names	Location	Structural Features	Postreceptor Mechanism
M_1		Nerves	Seven transmembrane segments, $G_{q/11}$ protein-linked	IP_3, DAG cascade
M_2	Cardiac M_2	Heart, nerves, smooth muscle	Seven transmembrane segments, $G_{i/o}$ protein-linked	Inhibition of cAMP production, activation of K^+ channels
M_3		Glands, smooth muscle, endothelium	Seven transmembrane segments, $G_{q/11}$ protein-linked	IP_3, DAG cascade
M_4		CNS	Seven transmembrane segments, $G_{i/o}$ protein-linked	Inhibition of cAMP production
M_5		CNS	Seven transmembrane segments, $G_{q/11}$ protein-linked	IP_3, DAG cascade

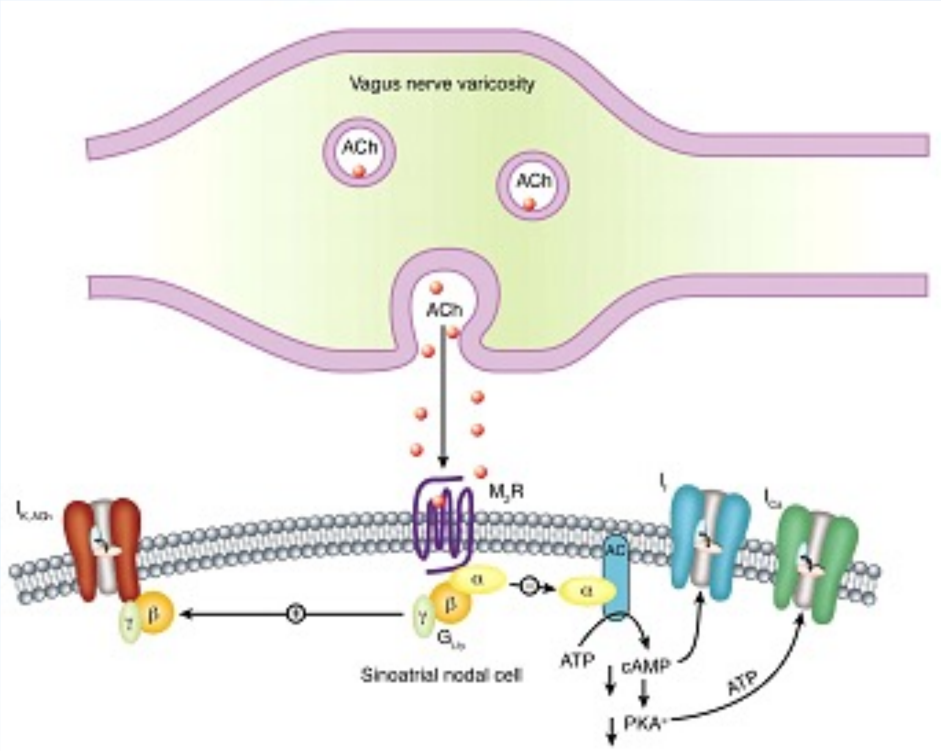
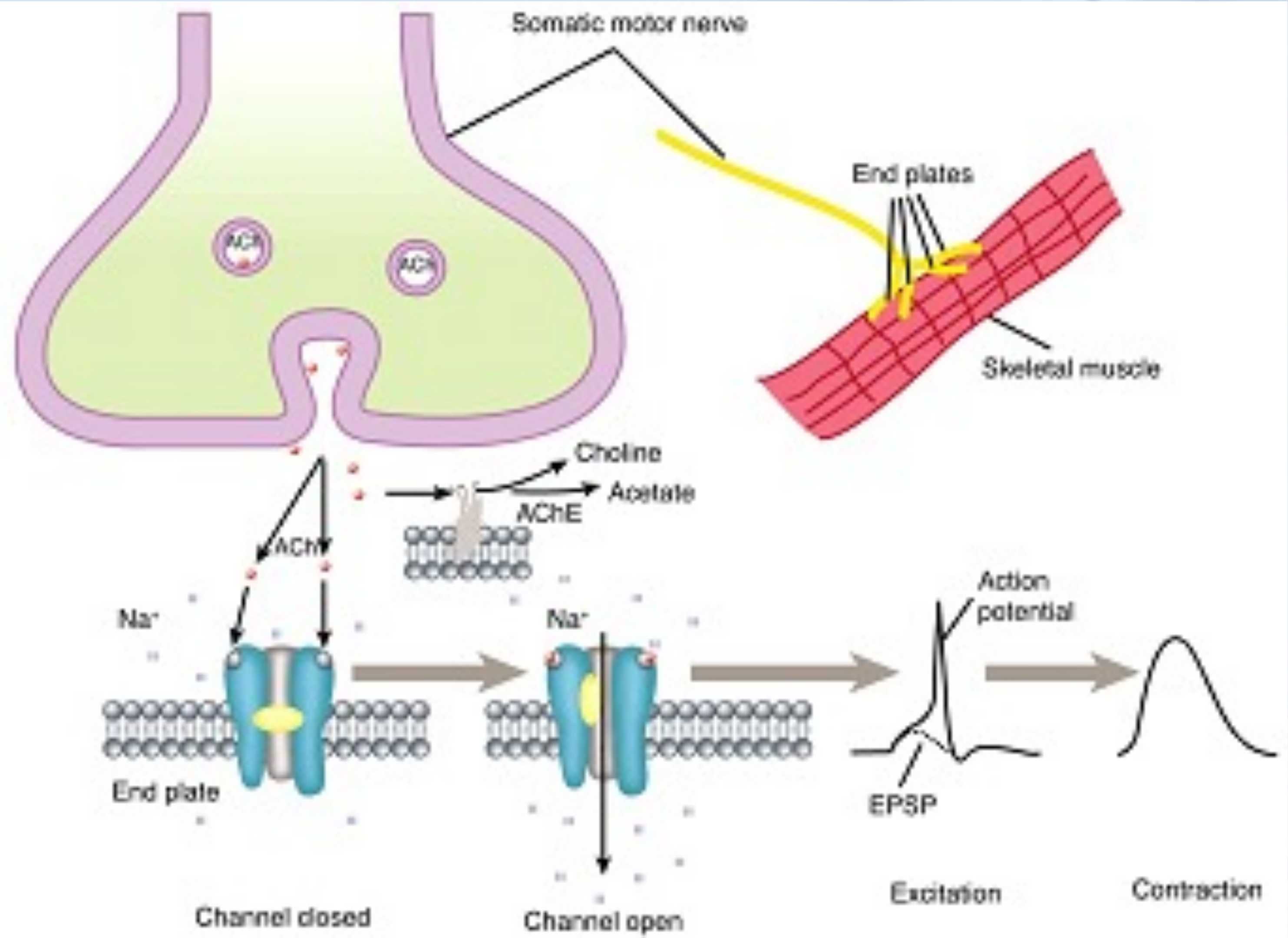
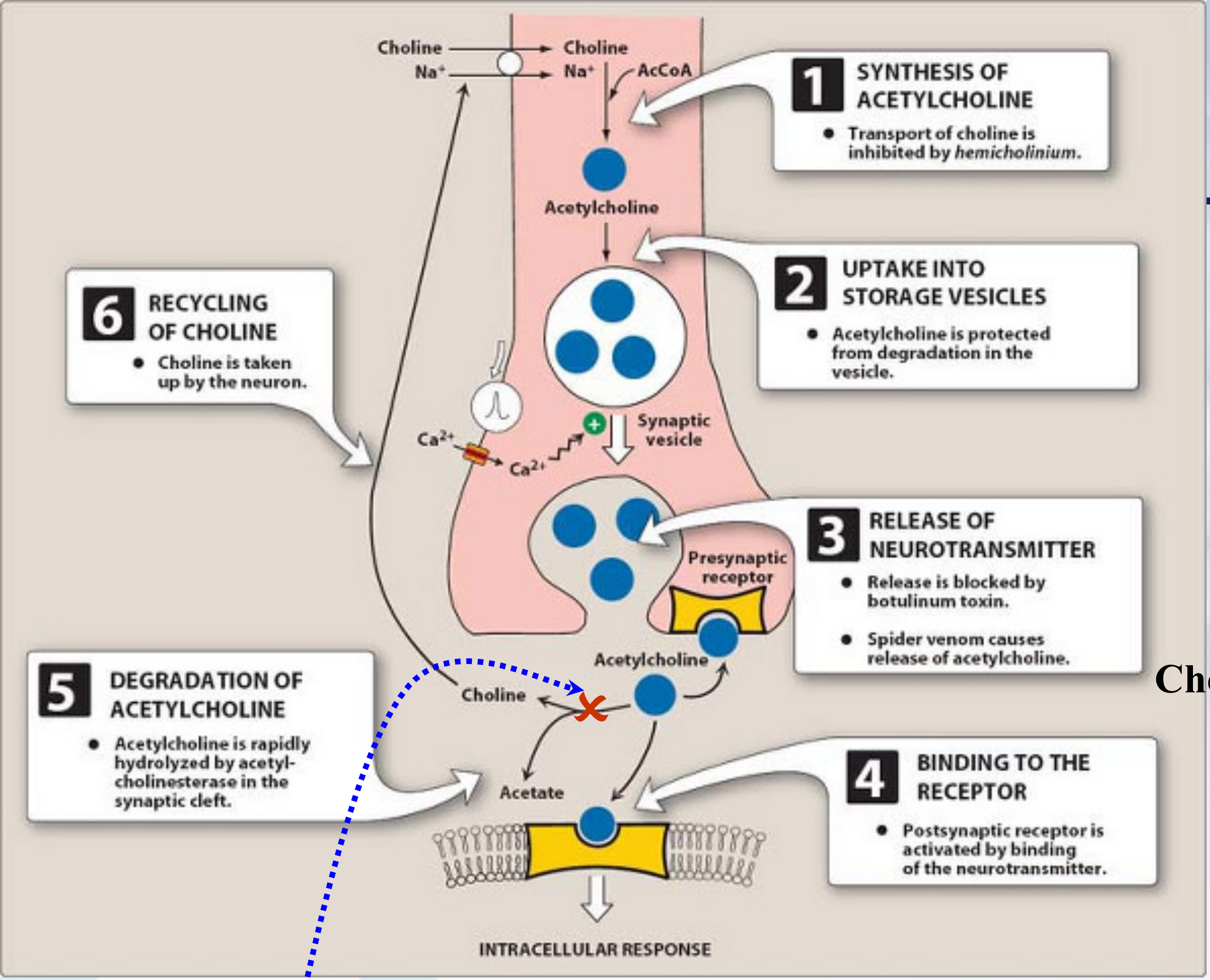


TABLE 7–1 Subtypes and characteristics of cholinoceptors.

Receptor Type	Other Names	Location	Structural Features	Postreceptor Mechanism
N_M	Muscle type, end plate receptor	Skeletal muscle neuromuscular junction	Pentamer $[(\alpha 1)_2\beta 1\delta\gamma]$	Na^+, K^+ depolarizing ion channel
N_N	Neuronal type, ganglion receptor	CNS postganglionic cell body, dendrites	Pentamer with α and β subunits only, eg, $(\alpha 4)_2(\beta 2)_3$ (CNS) or $\alpha 3\ \alpha 5(\beta 2)_3$ (ganglia)	Na^+, K^+ depolarizing ion channel



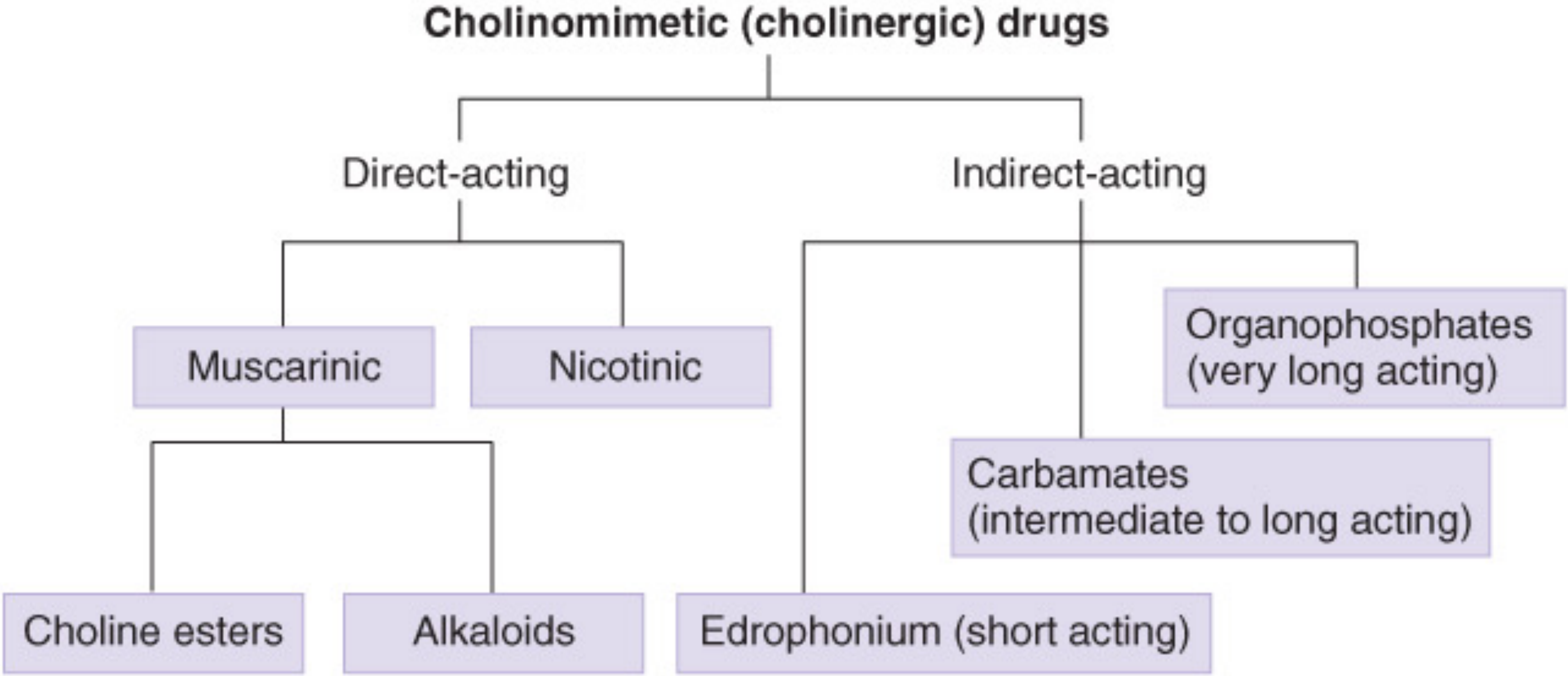


Direct-Acting Cholinoceptor Stimulants

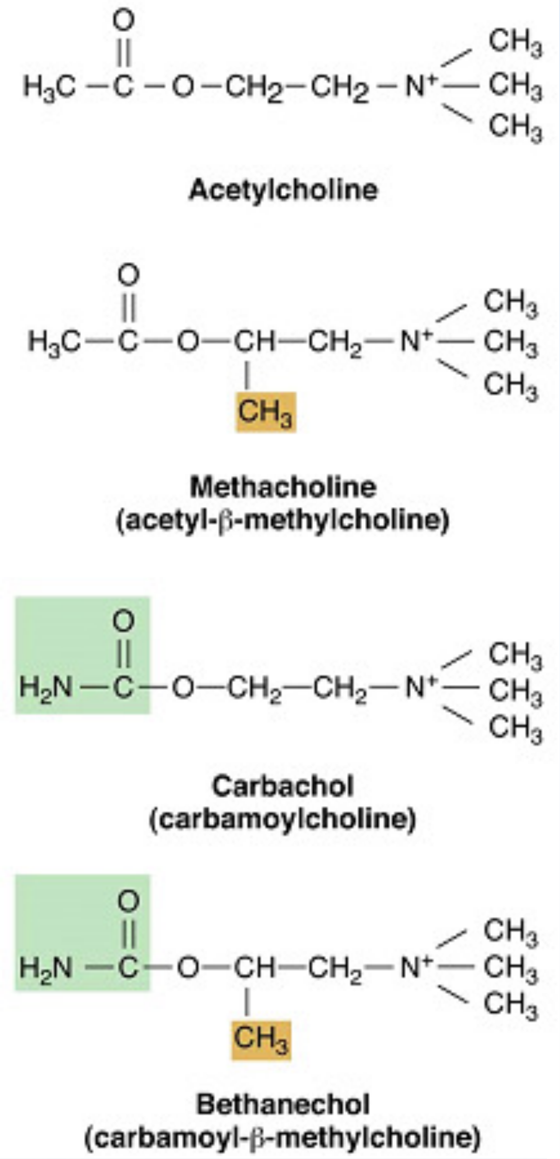
Indirect-Acting Cholinomimetics

Mode of Action of Cholinomimetic Drugs

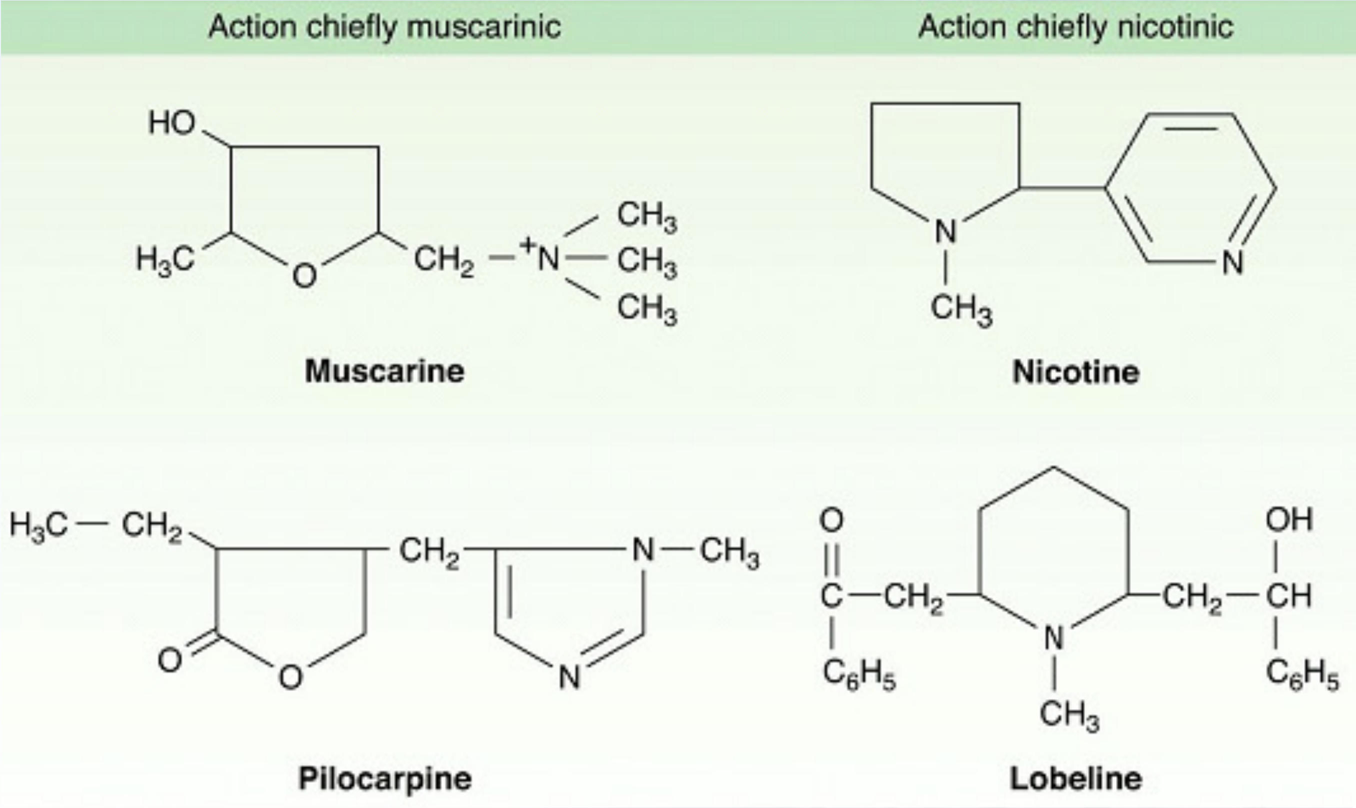
- Cholinomimetic Drugs
  ≈Parasympathomimetic drugs
  ≈ Cholinergic drugs
- Direct-Acting Cholinoceptor Stimulants
- Indirect-Acting Cholinomimetics
  - Anticholinesterases (Cholinesterase Inhibitors)
    - Reversible
  - Anticholinesterases (Cholinesterase Inhibitors)
    - Irreversible


Cholinomimetic (cholinergic) drugs
Direct-acting
Indirect-acting
Muscarinic
Nicotinic
Organophosphates (very long acting)
Carbamates (intermediate to long acting)
Choline esters
Alkaloids
Edrophonium (short acting)

Direct-Acting Cholinoceptor Stimulants



- The direct-acting cholinomimetic drugs can be divided on the basis of chemical structure into
  - esters of choline (including acetylcholine)
  - alkaloids (such as muscarine and nicotine).



Absorption, Distribution, and Metabolism

- Choline esters
  - are poorly absorbed and poorly distributed into the central nervous system because they are hydrophilic

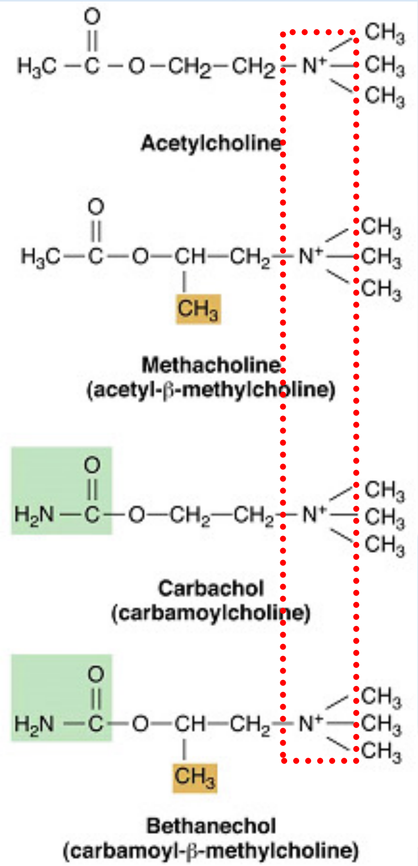
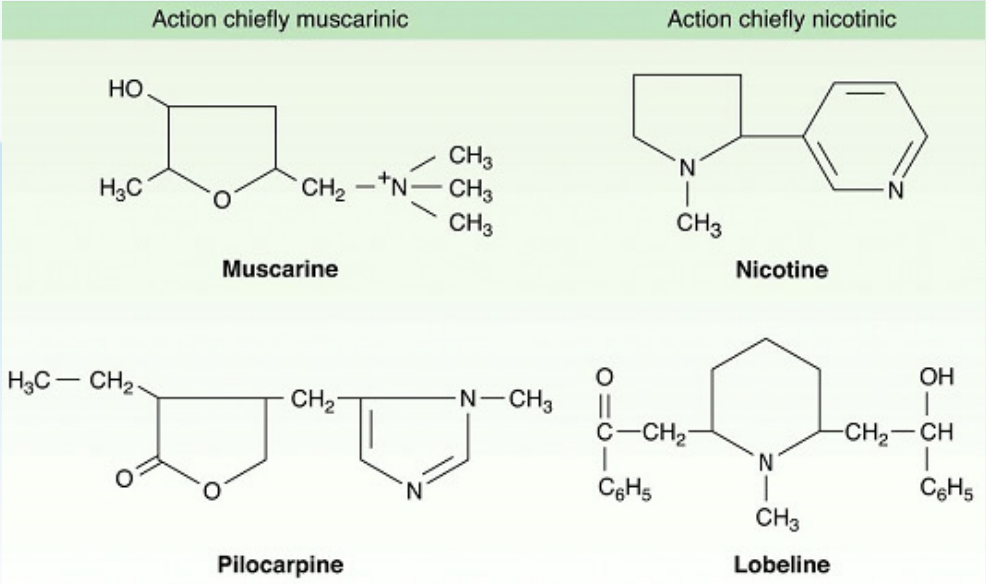


TABLE 7–2 Properties of choline esters.

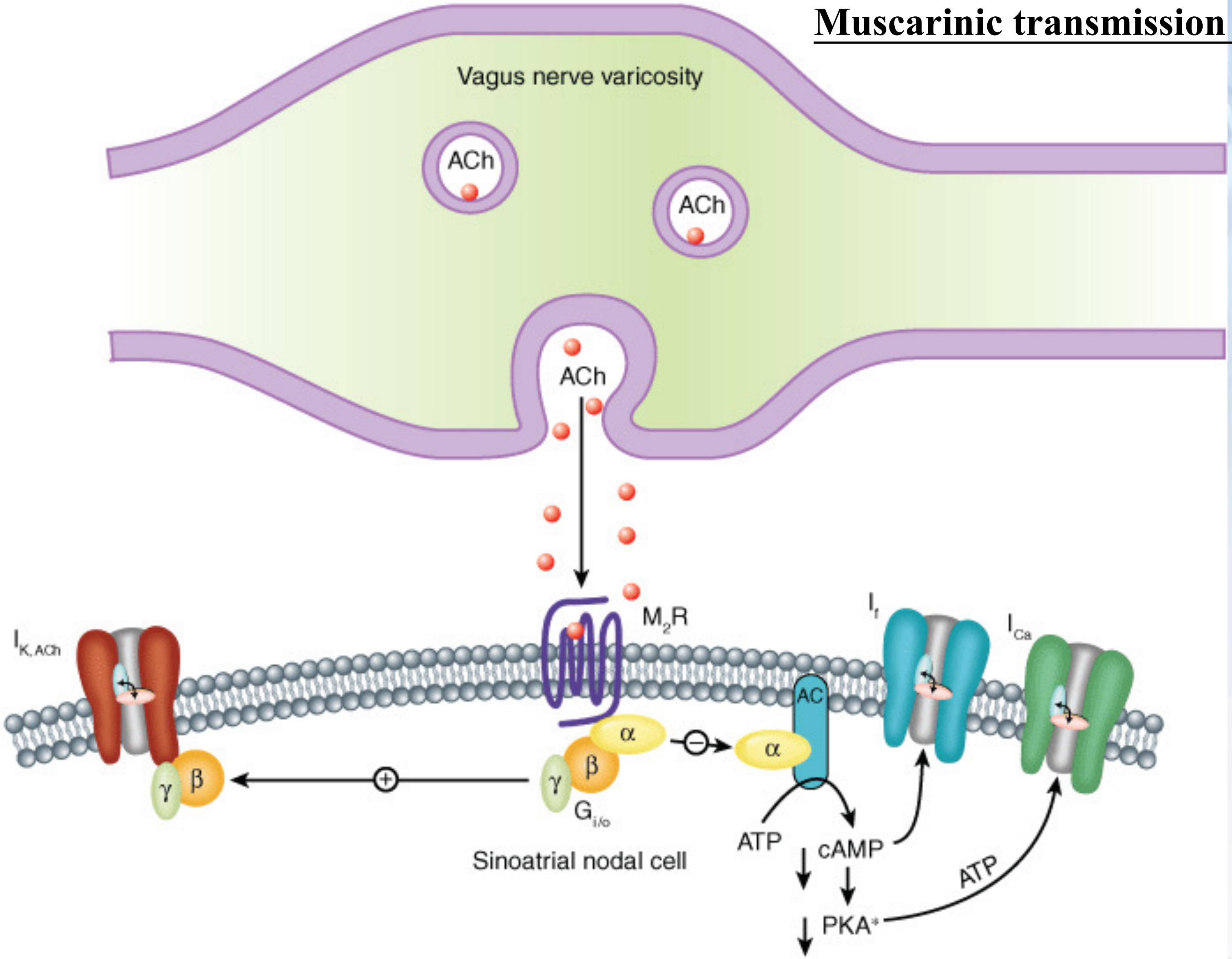
Choline Ester	Susceptibility to Cholinesterase	Muscarinic Action	Nicotinic Action
Acetylcholine chloride	++++	+++	+++
Methacholine chloride	+	++++	None
Carbachol chloride	Negligible	++	+++
Bethanechol chloride	Negligible	++	None

- The tertiary natural cholinomimetic alkaloids (pilocarpine, nicotine, lobeline) are well absorbed from most sites of administration.
  - Nicotine
    - a liquid, is sufficiently lipid-soluble to be absorbed across the skin
  - Muscarine
    - a quaternary amine, is less completely absorbed from the gastrointestinal tract than the tertiary amines but is nevertheless toxic when ingested—eg, in certain mushrooms—and it even enters the brain.

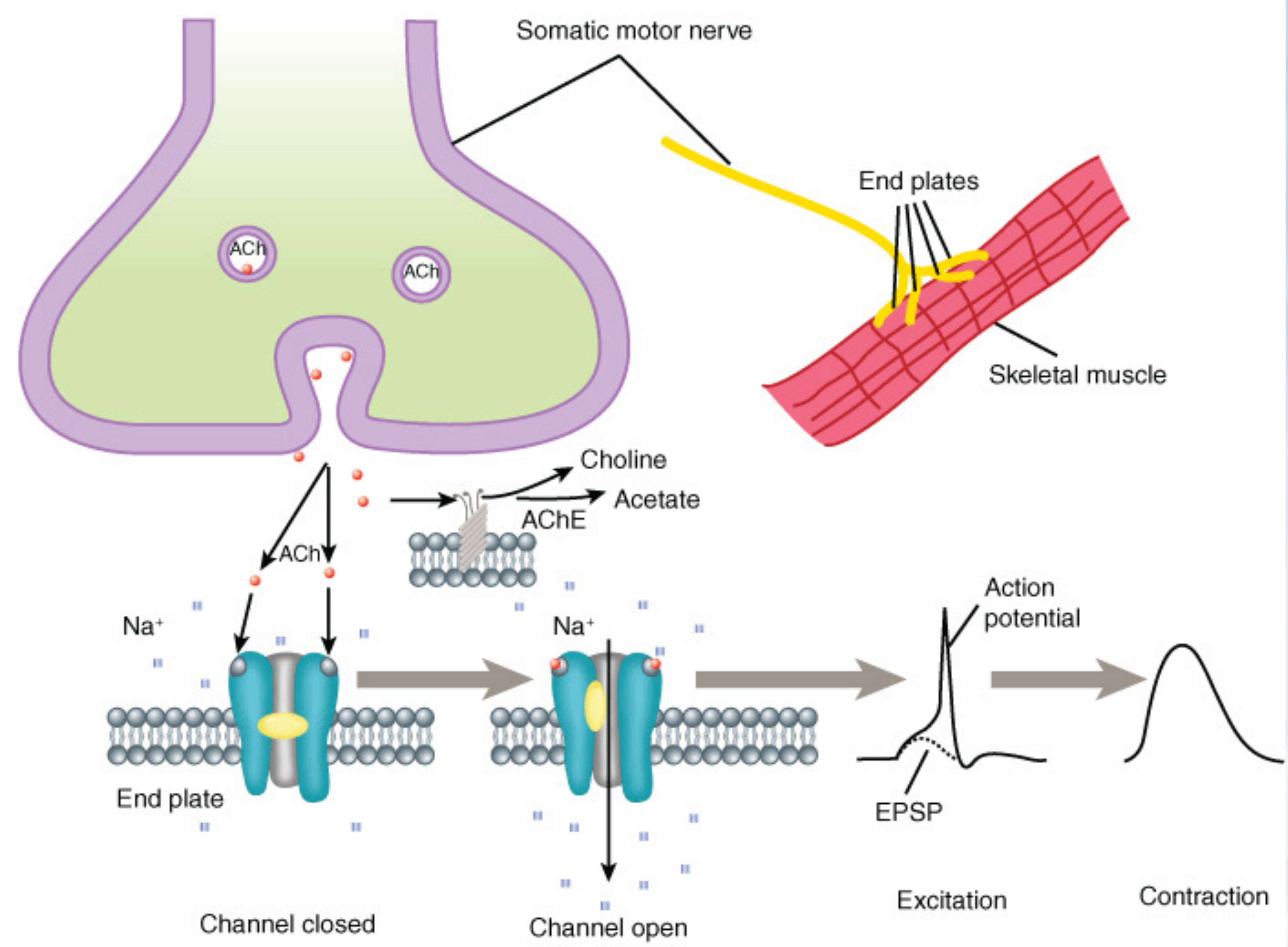


Mechanism of Action Direct-Acting Cholinoceptor Stimulants

Muscarinic transmission in heart



Nicotinic transmission at the skeletal neuromuscular junction



Organ System Effects

Direct-Acting Cholinoceptor Stimulants

Organ	Response
Eye	
Sphincter muscle of iris	Contraction (miosis)
Ciliary muscle	Contraction for near vision
Heart	
Sinoatrial node	Decrease in rate (negative chronotropy)
Atria	Decrease in contractile strength (negative inotropy). Decrease in refractory period
Atrioventricular node	Decrease in conduction velocity (negative dromotropy). Increase in refractory period
Ventricles	Small decrease in contractile strength
Blood vessels	
Arteries	Dilation (via EDRF). Constriction (high-dose direct effect)
Veins	Dilation (via EDRF). Constriction (high-dose direct effect)
Lung	
Bronchial muscle	Contraction (bronchoconstriction)
Bronchial glands	Stimulation

Organ System Effects

Direct-Acting Cholinoceptor Stimulants

Organ	Response
Gastrointestinal tract	
Motility	Increase
Sphincters	Relaxation
Secretion	Stimulation
Urinary bladder	
Detrusor	Contraction
Trigone and sphincter	Relaxation
Glands	
Sweat, salivary, lacrimal, nasopharyngeal	Secretion

Organ System Effects

- Eye
  - – aqueous humor outflow
- Cardiovascular System
  - – The primary cardiovascular effects of muscarinic agonists are reduction in
    - peripheral vascular resistance and changes in heart rate
- Respiratory System
  - – Muscarinic stimulants contract the smooth muscle of the bronchial tree. In addition, the glands of the tracheobronchial mucosa are stimulated to secrete

Organ System Effects

Direct-Acting Cholinoceptor Stimulants

- Gastrointestinal Tract
  - Administration of muscarinic agonists, as in parasympathetic nervous system stimulation,
    - secretory and motor activity of the gut ⬆
- Genitourinary Tract
  - stimulate detrusor muscle (逼尿肌)
  - relax sphincter muscles
- Central Nervous System
  - contains both muscarinic and nicotinic receptors
    - muscarinic > nicotinic

Organ System Effects

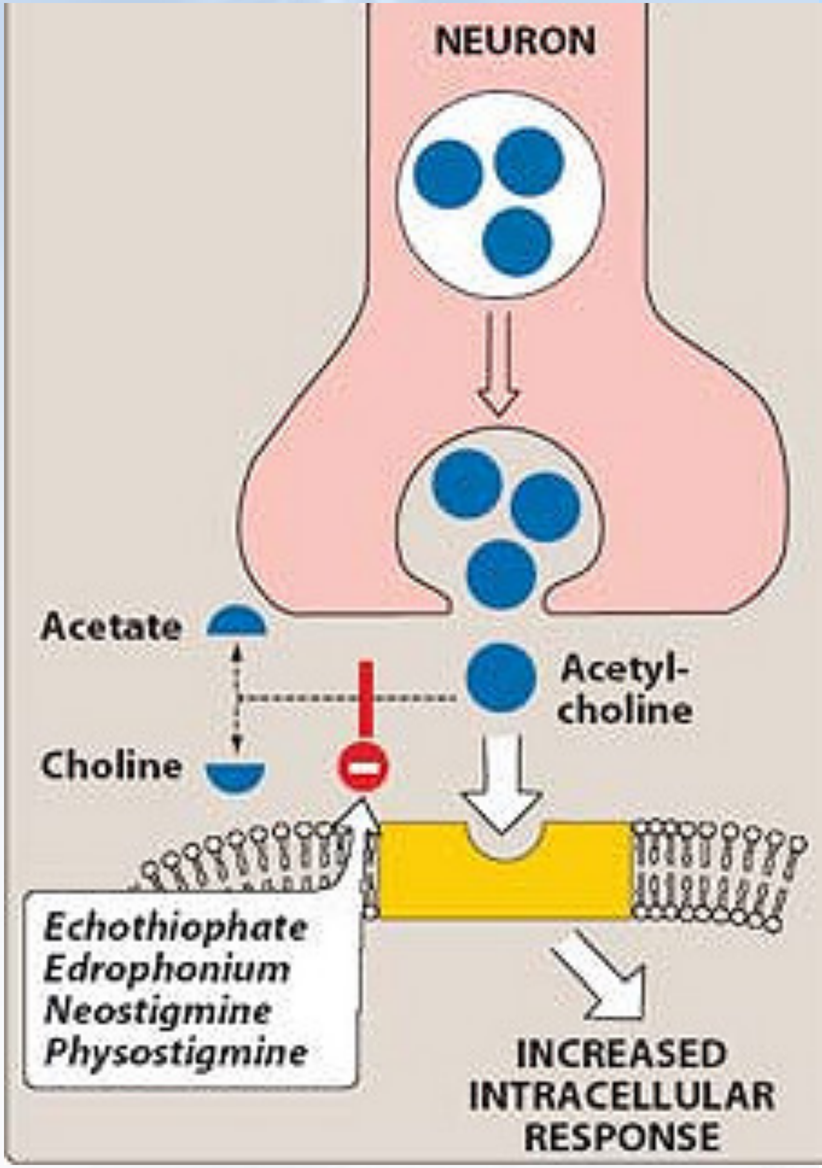
- Peripheral Nervous System
  - Autonomic ganglia are important sites of nicotinic synaptic action.
    - In the case of the cardiovascular system, the effects of nicotine are chiefly sympathomimetic
- Neuromuscular Junction
  - nicotinic agonist → sodium and potassium ions⬆→ depolarization →contractile response

Drugs Used for Cholinomimetic Effects

Subclass	**Mechanism of Action**	**Effects**	**Clinical Applications**	**Pharmacokinetics, Toxicities, Interactions**
Bethanechol	Muscarinic agonist	causes increased secretion, smooth muscle contraction (except vascular smooth muscle relaxes), and changes in heart rate	Postoperative and neurogenic ileus and urinary retention	*Interactions:* Additive with other parasympathomimetics
Carbachol: Nonselective muscarinic and nicotinic agonist; otherwise similar to bethanechol; used topically almost exclusively for glaucoma				
Direct-acting muscarinic alkaloids or synthetics				
Pilocarpine	Like bethanechol, partial agonist	Like bethanechol	Glaucoma	*Toxicity & interactions:* Like bethanechol
Direct-acting nicotinic agonists				
Nicotine	Agonist at both N_N and N_M receptors	enters CNS and activates N_N receptors	nonmedical use in smoking and in insecticides	*Interactions:* Additive with CNS stimulants

Indirect-Acting Cholinomimetics

- Anticholinesterases (Cholinesterase Inhibitors)
  – Reversible
  – Irreversible



Structure

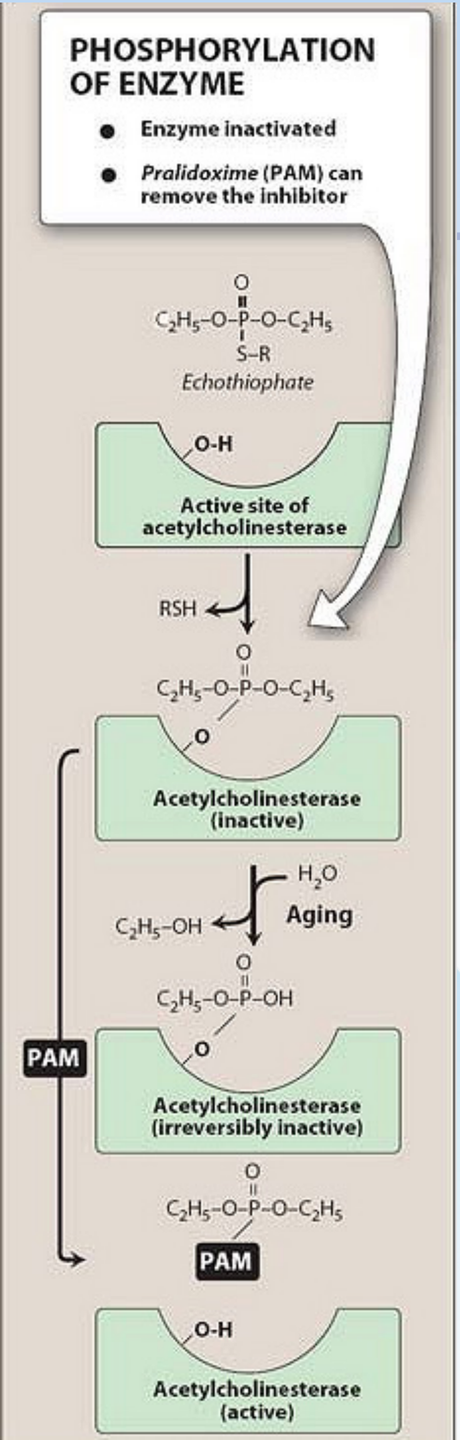
- There are three chemical groups of cholinesterase inhibitors

Reversible

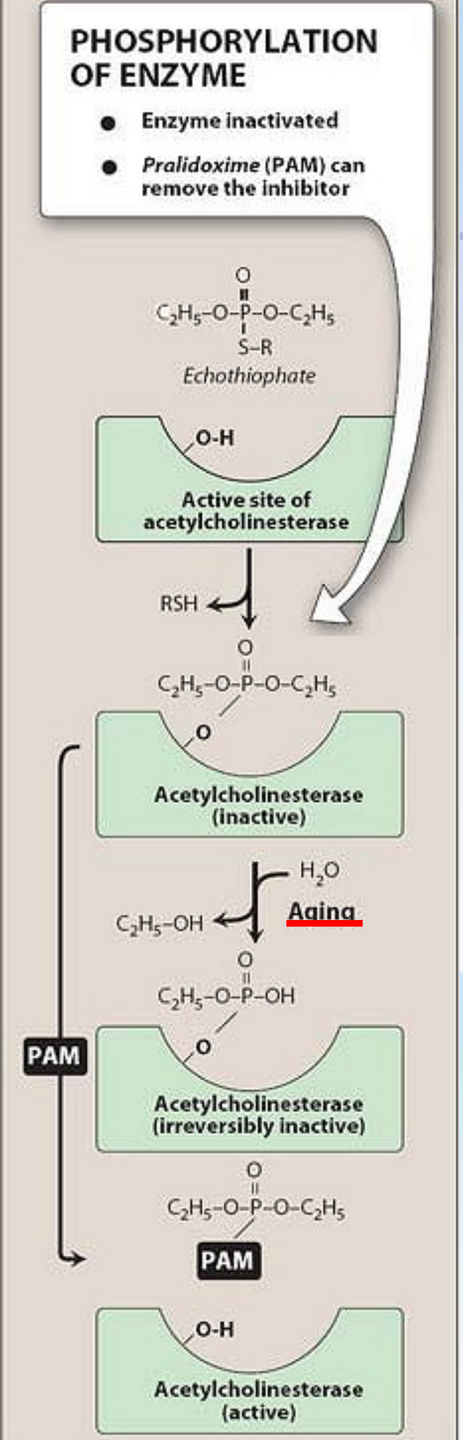
  - alcohols
    - Edrophonium
  - carbamates
    - Neostigmine, Pyridostigmine, Physostigmine , Ambenonium, Demecarium

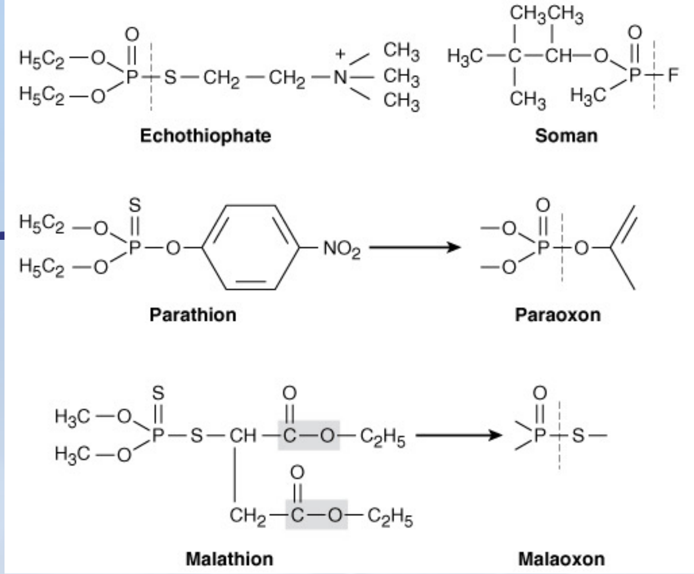
Irreversible

  - Organophosphates
    - Echothiophate
    - Malathion
    - Parathion
    - Sarin



- Malathion
  - and a few other organophosphate insecticides are also rapidly metabolized by other pathways to inactive products in birds and mammals but not in insects; these agents are therefore considered safe enough for sale to the general public.
- Parathion
  - is not detoxified effectively in vertebrates; thus, it is considerably more dangerous than malathion to humans and livestock and is not available for general public use in the USA.





- **Aging**
  - before aging has occurred, strong nucleophiles like pralidoxime are able to break the phosphorus-enzyme bond and can be used as "cholinesterase regenerator”

	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
Short-acting cholinesterase inhibitor				
Edrophonium	Alcohol, binds briefly to active site of acetylcholinesterase (AChE) and prevents access of acetylcholine (ACh)	Amplifies all actions of ACh increases parasympathetic activity and somatic neuromuscular transmission	Diagnosis and acute treatment of myasthenia gravis	Parenteral quaternary amine does not enter CNS *Toxicity:* Parasympathomimetic excess *Interactions:* Additive with parasympathomimetics
Intermediate-acting cholinesterase inhibitors				
Neostigmine	Forms covalent bond with AChE, but hydrolyzed and released	Like edrophonium, but longer-acting	Myasthenia gravis postoperative and neurogenic ileus and urinary retention	Oral and parenteral; quaternary amine, does not enter CNS. Duration 2–4 h *Toxicity and Interactions:* Like edrophonium
Pyridostigmine: Like neostigmine, but longer-acting (4–6 h); used in myasthenia				
Physostigmine: Like neostigmine, but natural alkaloid tertiary amine; enters CNS				
Long-acting cholinesterase inhibitors				
Echothiophate	Like neostigmine, but released more slowly	Like neostigmine, but longer-acting	Obsolete was used in glaucoma	Topical only *Toxicity:* Brow ache, uveitis, blurred vision
Malathion: Insecticide, relatively safe for mammals and birds because metabolized by other enzymes to inactive products; some medical use as ectoparasiticide				
Parathion, others: Insecticide, dangerous for all animals; toxicity important because of agricultural use and exposure of farm workers (see text)				
Sarin, others: "Nerve gas," used exclusively in warfare and terrorism				

Organ System Effects Indirect-Acting Cholinomimetics

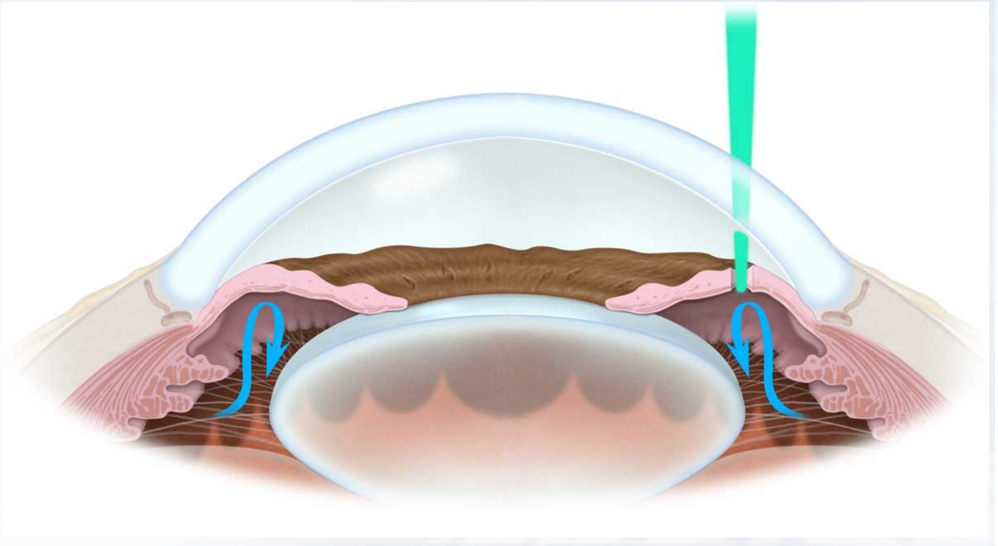
- Central Nervous System
- Eye, Respiratory Tract, Gastrointestinal Tract, Urinary Tract
- Cardiovascular System
- Neuromuscular Junction
  - Low (therapeutic) concentrations→acetylcholine⬆ → contraction ⬆
  - especially in muscles weakened
    - curare-like neuromuscular blocking agents
    - myasthenia gravis

Clinical Uses Cholinomimetics

- The Eye
  - glaucoma was treated with
    - direct agonists
      - pilocarpine, methacholine, carbachol
    - cholinesterase inhibitors
      - physostigmine, demecarium, echothiophate, isoflurophate
  - For chronic glaucoma, these drugs have been largely replaced by
    - beta-blockers
    - prostaglandin derivatives.

青光眼(Glaucoma)之治療

- 增加眼房水吸收
  - 如Physostigmine
- 減少眼房水形成
  - 使用β-blocker（如Timolol）、碳酸酐酶抑制劑（如Acetazolamide）、高滲透性利尿劑（如Mannitol）及腎上腺素(Epinephrine)。
- 促進房水的流出
  - Pilocarpine、Latanoprost(Xalatan®)
- 外科手術（如放射療法）



- Gastrointestinal and Urinary Tracts
  - postoperative ileus (術後腸阻塞)
  - Urinary retention
  - Of the choline esters, bethanechol is the most widely used for these disorders
  - Of the cholinesterase inhibitors, neostigmine is the most widely used for these applications (subcutaneously in a dose of 0.5–1 mg)

Note: the clinician must be certain that there is no mechanical obstruction to outflow before using the cholinomimetic.

- Neuromuscular Junction
  - Edrophonium is sometimes used as a diagnostic test for myasthenia
  - Long-term therapy for myasthenia gravis is usually accomplished with pyridostigmine; neostigmine or ambenonium are alternatives
    - The doses are titrated to optimum levels based on changes in muscle strength

- Heart
  - In this application(supraventricular tachyarrhythmias), edrophonium has been replaced by newer drugs (adenosine and the calcium channel blockers verapamil and diltiazem).
- Antimuscarinic Drug Intoxication
  - Physostigmine has been used for this application because it enters the central nervous system and reverses the central as well as the peripheral signs of muscarinic blockade

Summary (1)

Subclass	Mechanism of Action	Clinical and Other Applications	Pharmacokinetics	Toxicities, Interactions
Direct-acting, muscarinic agonists				
Bethanechol	Activates muscarinic (M) receptors; increases IP_3 and DAG	Bladder and bowel atony, for example, after surgery or spinal cord injury	Oral, IM activity Poor lipid solubility: does not enter CNS; not active in eye after topical application Duration: 0.3–2 h	All parasympathomimetic effects: cyclospasm, diarrhea, urinary urgency, plus vasodilation, reflex tachycardia, and sweating
Pilocarpine	Same as bethanechol	Sjögren's syndrome (increases salivation); was used in glaucoma (causes miosis, cyclospasm)	Oral, IM activity Good lipid solubility, topical activity in eye	Similar to bethanechol but may cause vasoconstriction via ganglionic effect
Muscarine	Same as bethanechol	Alkaloid found in mushrooms	Low lipid solubility but readily absorbed from gut	Mushroom poisoning of fast-onset type

Summary (2)

Subclass	Mechanism of Action	Clinical and Other Applications	Pharmacokinetics	Toxicities, Interactions
Direct-acting, nicotinic agonists				
Nicotine	Activates all nicotinic (N) receptors; opens Na-K channels in ganglia and neuromuscular end plates	Smoking cessation (also used as insecticide)	High lipid solubility, absorbed by all routes For smoking cessation: usually used as gum or transdermal patch Duration: 4–6 h	Generalized ganglionic stimulation: hypertension, tachycardia, nausea, vomiting, diarrhea Major overdose: convulsions, paralysis, coma
Varenicline	A partial agonist at N receptors	Smoking cessation	High lipid solubility, oral activity Duration: ~12 h	Hypertension, sweating, sensory disturbance, diarrhea, polyuria, menstrual disturbance
Succinylcholine	N-receptor agonist, moderately selective for neuromuscular (NM) end plate	N_M relaxation (see Chapter 27)	Highly polar, used IV Duration: 5–10 min	Initial muscle spasms and postoperative pain Prolonged action in persons with abnormal butyrylcholinesterase

Summary (3)

Subclass	Mechanism of Action	Clinical and Other Applications	Pharmacokinetics	Toxicities, Interactions
Indirect-acting				
Edrophonium	Inhibitor of cholinesterase	diagnosis of myasthenia gravis	used IV Duration: 5–10 min	Increased parasympathetic effects, especially nausea, vomiting, diarrhea, urinary urgency
Neostigmine	Like edrophonium	Reversal of N_M block, treatment of myasthenia	Moderately polar but orally active Duration: 2–4 h	Like edrophonium but longer duration
Pyridostigmine	Like edrophonium	Treatment of myasthenia	Moderately polar but orally active Duration: 4–8 h	Like edrophonium but longer duration
Physostigmine	Like edrophonium	Reversal of severe atropine poisoning (IV)	Lipid soluble; can be used topically in the eye Duration: 2–4 h	Like edrophonium but longer duration plus CNS effects: seizures

Summary (4)

Subclass	Mechanism of Action	Clinical and Other Applications	Pharmacokinetics	Toxicities, Interactions
Indirect-acting (organophosphate)				
Parathion	Like edrophonium	Insecticide only Duration: days to weeks	Highly lipid-soluble	Highly dangerous insecticide; causes all parasympathetic effects plus muscle paralysis and coma
Malathion	Like edrophonium	Insecticide and scabicide (topical) Duration: days	Highly lipid-soluble but metabolized to inactive products in mammals and birds	Much safer insecticide than parathion
Sarin, tabun, others	Like parathion	Nerve gases; terrorist threat	Like parathion but more rapid action	Rapidly lethal

Summary (5)

Subclass	Mechanism of Action	Clinical and Other Applications	Pharmacokinetics	Toxicities, Interactions
Indirect-acting, for Alzheimer's disease				
Rivastigmine, galantamine, donepezil, tacrine (obsolete)	Cholinesterase inhibition plus variable other poorly understood effects	Alzheimer's disease	Lipid soluble, enter CNS Half-lives: 1.5–70 h	Nausea, vomiting

Chapter 8

Cholinoceptor-Blocking Drugs

藥理學報告

- 期刊選擇
  - The New England journal of medicine
  - Nature medicine
  - JAMA, the Journal of the American Medical Association
  - The lancet (馬兜鈴酸)
  - Nature reviews. Drug discovery
  - Pharmacological reviews
  - Clinical pharmacology and therapeutics
  - …..
- 撰寫格式(中英文皆可)
  - 摘要
  - 前言
  - 結果
  - 討論
  - 心得

overview

Antimuscarinic

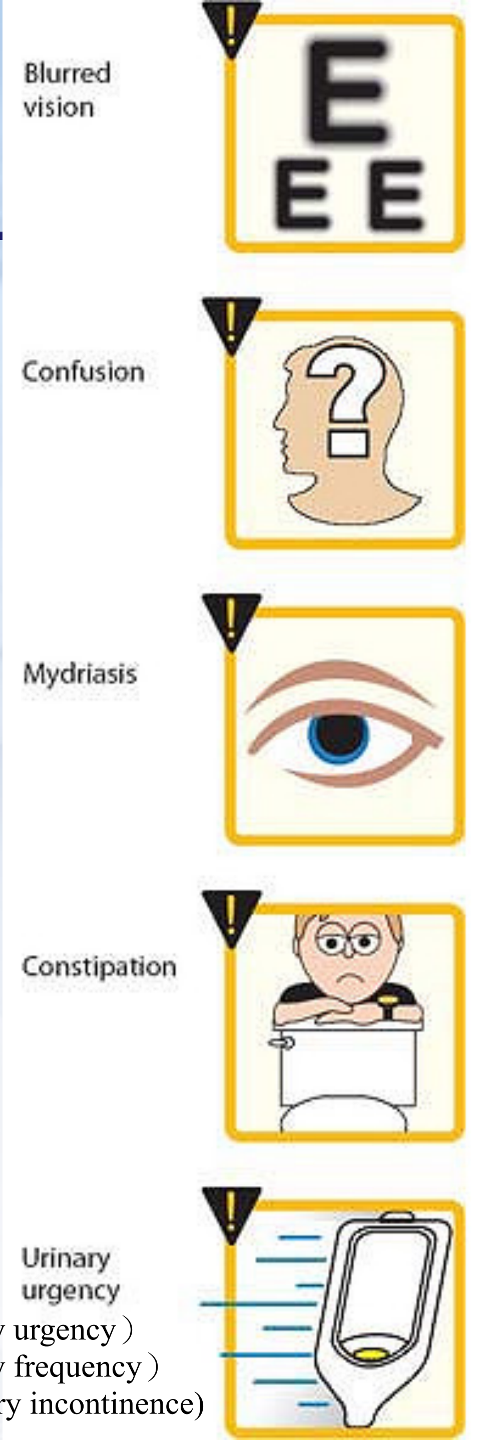
Atropine, Scopolamine, Benztropine
Homatropine, cyclopentolate, tropicamide
Ipratropium, tiotropium
Dicyclomine, glycopyrrolate
Oxybutynin, Trospium
Tolterodine, fesoterodine, Darifenacin, solifenacin,
Pirenzepine,telenzepine

Ganglion blocker

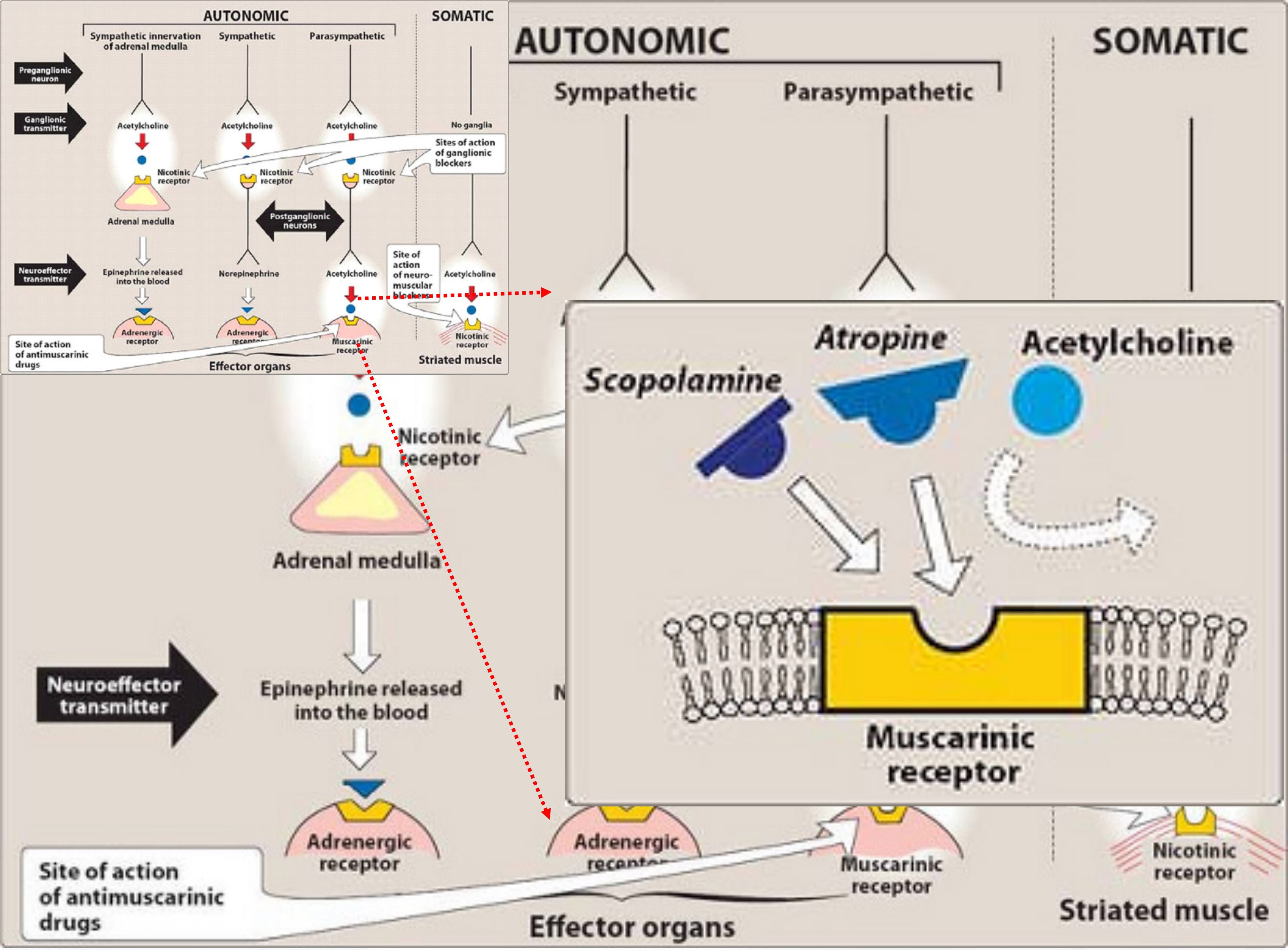
Hexamethonium, Trimethaphan, Mecamylamine

Neuronuscular blocker

Succinylcholine
d-Tubocurarine
Cistracurium
Mivacurium
Rocuronium
Vecuronium



尿急（urinary urgency）
尿頻（urinary frequency）
尿失禁(uninary incontinence)



AUTONOMIC
SOMATIC
Sympathetic innervation of adrenal medulla
Sympathetic
Parasympathetic
Preganglionic neuron
Ganglionic transmitter
Acetylcholine
Acetylcholine
Acetylcholine
No ganglia
Sites of action of ganglionic blockers
Nicotinic receptor
Nicotinic receptor
Nicotinic receptor
Adrenal medulla
Postganglionic neurons
Site of action of neuro-muscular blockers
Neuroeffector transmitter
Epinephrine released into the blood
Norepinephrine
Acetylcholine
Acetylcholine
Adrenergic receptor
Adrenergic receptor
Muscarinic receptor
Nicotinic receptor
Site of action of antimuscarinic drugs
Effector organs
Striated muscle
AUTONOMIC
SOMATIC
Sympathetic
Parasympathetic
Nicotinic receptor
Adrenal medulla
Neuroeffector transmitter
Epinephrine released into the blood
Adrenergic receptor
Adrenergic
Muscarinic receptor
Nicotinic receptor
Site of action of antimuscarinic drugs
Effector organs
Striated muscle
Atropine
Acetylcholine
Scopolamine
Muscarinic receptor

Introduction

- cholinergic antagonists also called
  - cholinergic blockers
  - parasympatholytics
  - anticholinergic drugs
- Cholinoceptor antagonists, like agonists, are divided into
  - muscarinic and nicotinic subgroups on the basis of their specific receptor affinities
    - Muscarinic antagonists (✓) are sometimes called parasympatholytic

Source

顛茄Atropa belladonna-Solanaceae

Atropine (hyoscyamine;莨菪鹼)

曼陀羅Datura stramonium-Solanaceae

Scopolamine (hyoscine;東莨菪鹼)

Distribution, Metabolism and Excretion

- Scopolamine is rapidly and fully distributed into the CNS where it has greater effects than most other antimuscarinic drugs
- Atropine
  - Effects on the iris and ciliary muscle persist for ≧72 hours

Organ System Effects Cholinoceptor-Blocking Drugs

- Central Nervous System
  - In the doses usually used
    - Scopolamine ＞atropine
      - Scopolamine：Drowsiness(睡意), amnesia
  - In toxic doses
    - scopolamine, and to a lesser degree atropine, can cause excitement, agitation, hallucinations, and coma
- Eye
  - Mydriasis
  - contraction of the ciliary muscle ⬇, or cycloplegia (睫狀肌麻痺)
  - lacrimal (淚腺) secretion ⬇

- Cardiovascular System
  - cardiovascular effects (atropine) are not dramatic
    - tachycardia may occur, but there is little effect on blood pressure.
- Respiratory System
  - atropine → bronchodilation and secretion⬇
  - treatment of asthma
    - antimuscarinic drugs 不如beta-adrenoceptor stimulants有效
  - antimuscarinic agents are valuable in some patients with asthma or COPD (chronic obstructive pulmonary disease)

- Gastrointestinal Tract
  - Blockade of muscarinic receptors has dramatic effects on motility and some of the secretory functions of the gut
  - Antimuscarinic drugs have marked effects on salivary secretion
    - Dry mouth 明顯
    - Gastric secretion比較不明顯
    - Pirenzepine, telenzepine
      - reduce gastric acid secretion明顯
        - » But, are investigational in the USA

Hyoscine butylbromide (Buscopan®)

- 副作用：
  1.眼睛偶爾會發生調節障礙
  2.偶爾心悸亢進、排尿障礙、口渴、便秘偶有腹部膨滿感、頭重感、頭痛等症狀
  3.若有發疹等現象，應立即停藥
- 注意事項：
  1.只有在嚴密觀察下，懷孕前3個月的婦女才可使用
  2.使用本藥後，開車和操作機械時應小心
  3.鬱血性心不全、心律不整、潰瘍性大腸炎、前列腺肥大症、甲狀腺機能亢進、處於高溫環境的病患，應謹慎用藥
- 使用禁忌：
  嚴重心臟病、痲痺性腸塞、青光眼、前列腺肥大引起的排尿障礙症、對本藥過敏患者
- 交互作用：
  與Phenothiazine系藥物、Monoamine Oxidase拮抗劑、三環系抗抑鬱劑、抗組織安劑併用時，會使增強本藥作用

- Genitourinary Tract
  - relaxes smooth muscle of the ureters(輸尿管) and bladder wall and slows voiding
  - it can precipitate urinary retention in men who have prostatic hyperplasia
  - The antimuscarinic drugs have no significant effect on the uterus

Therapeutic Applications

- Central Nervous System Disorders
- Ophthalmologic Disorders
- Respiratory Disorders
- Cardiovascular Disorders
- Gastrointestinal Disorders
- Urinary Disorders

- Central Nervous System Disorders
  - Parkinson's disease
  - Motion Sickness
    - Scopolamine
      - Useful doses by any route usually cause significant sedation and dry mouth
- Ophthalmologic Disorders

Drug	Duration of Effect (days)	Usual Concentration (%)
Atropine	7–10	0.5–1
Scopolamine	3–7	0.25
Homatropine	1–3	2–5
Cyclopentolate	1	0.5–2
Tropicamide	0.25	0.5–1

- Respiratory Disorders
  - atropine →預防 anesthetics (ether were used) → increased airway secretions
  - Ipratropium (Atrovent®)
    - Be useful in
      - Asthma, COPD
- Gastrointestinal Disorders
  - Antimuscarinic agents are now rarely used for peptic ulcer disease in the USA

- Urinary Disorders
  - Oxybutynin
    - relieve bladder spasm after urologic surgery(泌尿外科), eg, prostatectomy
  - Trospium
  - Darifenacin and solifenacin
    - once-daily dosing because of their long half-lives
  - Tolterodine and fesoterodine
    - urinary incontinence(尿失禁)

- 尿失禁
  - 最常被使用的此類藥物為oxybutynin及tolterodine
  - 二線治療藥物 imipramine, propantheline dicyclomine

- Cholinergic Poisoning
  - atropine
    - Large doses of atropine may be needed to oppose the muscarinic effects of extremely potent agents like parathion and chemical warfare nerve gases
  - Cholinesterase Regenerator Compounds
    - pralidoxime (PAM)
    - diacetylmonoxime (DAM)
  - Against excessive acetylcholinesterase inhibition (irreversible organophosphate inhibitor) is *pretreatment* with reversible enzyme inhibitors
    - pyridostigmine (事先給予預防有機磷再與酵素鍵結)

Adverse Effects Muscarinic Receptor-Blocking Drugs

- At higher concentrations, atropine causes
  - Hallucinations, dry mouth, mydriasis, tachycardia, hot and flushed skin, agitation(激動), and delirium(譫妄)
    - hyperthermic effects of atropine
      - especially infants
- Overdoses of atropine are generally treated symptomatically
  - physostigmine (必要時)
  - Symptomatic treatment may require temperature control with cooling blankets and seizure control with diazepam

Contraindications

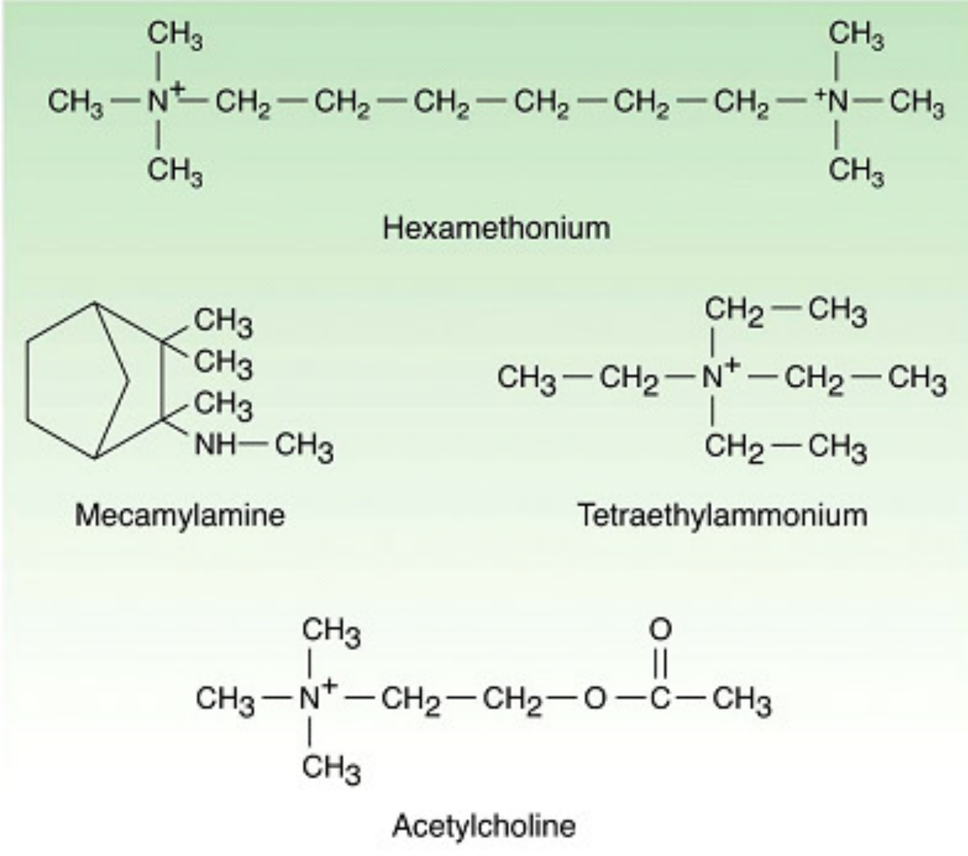
- Glaucoma
  - especially angle-closure glaucoma
- should be avoided in those
  - with a history of prostatic hyperplasia
- gastric ulcer
  - Because the antimuscarinic drugs slow gastric emptying

Basic & Clinical Pharmacology of the Ganglion-Blocking Drugs

- Ganglion-blocking agents
  - competitively block the action of acetylcholine and similar agonists at nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia
- Block all autonomic outflow
  - lack of selectivity confers such a broad range of undesirable effects that they have limited clinical use

Chemistry & Pharmacokinetics

- Tetraethylammonium (TEA)
- Hexamethonium ("C6")
  - the first drug effective for management of hypertension
- Mecamylamine
- Trimethaphan
  - intravenous infusion



The toxicity of the ganglion-blocking drugs is limited to the autonomic effects already described. For most patients, these effects are intolerable except for acute use.

Subclass	Mechanism of Action	Clinical Applications	Pharmacokinetics	Toxicities, Interactions
Antimuscarinic, nonselective				
Atropine	antagonist at all M receptors	Mydriatic, cycloplegic(睫狀肌麻痺); antidote for cholinesterase inhibitor toxicity	Lipid-soluble Duration: 2-4 h except in eye: 72 h	All parasympatholytic effects plus sedation, delirium, hyperthermia
Scopolamine: Anti-motion sickness via transdermal patch Benztropine: Antiparkinsonism Homatropine, cyclopentolate, tropicamide: Topical ophthalmic use to produce mydriasis, cycloplegia Ipratropium, tiotropium: Inhaled for asthma, chronic obstructive pulmonary disease Dicyclomine, glycopyrrolate: Oral, parenteral for gastrointestinal applications Oxybutynin: Oral, transdermal, promoted for urinary urgency, incontinence Trospium: Oral, for urinary urgency				
Antimuscarinic, selective				
Darifenacin, fesoterodine, solifenacin, tolterodine	Like atropine, but modest selectivity for M_3 receptors	Urinary urgency, incontinence	Oral Duration: 12-24 h	Excessive parasympatholytic effects
Pirenzepine, telenzepine	Significant M_1 selectivity	Peptic disease (not available in USA)	Oral	Excessive parasympatholytic effects
Antinicotinic ganglion blockers				
Hexamethonium	Selective block of N_N receptors	Obsolete; was used for hypertension	Oral, parenteral	Block of all autonomic effects
Trimethaphan: IV only, short-acting; was used for hypertensive emergencies and controlled hypotension Mecamylamine: Oral, enters CNS; investigational use for smoking cessation				
Antinicotinic neuromuscular blockers				
Regenerator				
Pralidoxime	Chemical antagonist of organophosphates	Organophosphate poisoning	Parenteral	Muscle weakness

Chapter 6 -Case Study

- A teenage boy is seen at the office of a dental surgeon for extraction of an impacted wisdom tooth. He is so nervous that the dentist decides to administer a sedative to calm the boy. After intravenous administration of the sedative (promethazine), the boy relaxes and the extraction is accomplished with no complications. However, when the boy stands up from the dental chair, he turns very pale and faints. Lying on the floor, he rapidly regains consciousness, but has a rapid heart rate of 120 bpm and a blood pressure of only 110/70 mm Hg. When he sits up, **his heart rate increases to 140 bpm, his pressure drops to 80/40 mm Hg**, and he complains of faintness. He is helped to a couch in the reception area, where he rests for 30 minutes. At the end of this time the boy is able to sit up without symptoms and, after an additional 15 minutes, is able to stand without difficulty. What autonomic effects might promethazine have that would explain the patient's signs and symptoms? Why did his heart rate increase when his blood pressure dropped ?

Chapter 7 -Case Study

- In mid-afternoon, a coworker brings 43-year-old JM to the emergency department because he is unable to continue picking vegetables. His gait is unsteady and he walks with support from his colleague. JM has difficulty speaking and swallowing, his vision is blurred, and his eyes are filled with tears. His coworker notes that JM was working in a field that **had been sprayed early in the morning with a material that had the odor of sulfur**. Within 3 hours after starting his work, JM complained of tightness in his chest that made breathing difficult, and he called for help before becoming disoriented.
- How would you proceed to evaluate and treat JM? What should be done for his coworker?

Chapter 8 -Case Study

- JH, a 63-year-old architect, complains of urinary symptoms to his family physician. He has hypertension and the last 8 years, he has been adequately managed with a thiazide diuretic and an angiotensin-converting enzyme inhibitor. During the same period, JH developed the signs of **benign prostatic hypertrophy**, which eventually required prostatectomy to relieve symptoms. He now complains that **he has an increased urge to urinate as well as urinary frequency**, and this has disrupted the pattern of his daily life. What do you suspect is the cause of JH's problem? What information would you gather to confirm your diagnosis? What treatment steps would you initiate?

Thank You!